

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
October 29-30, 2014
Atlanta, Georgia**

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Kent "Oz" Nelson Auditorium

Atlanta, Georgia 30333

October 29-30, 2014

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Wednesday, October 29th</u>		
8:00 Welcome & Introductions		Dr. Jonathan Temte (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
Remarks		Dr. Thomas Frieden, Director, CDC
8:30 <u>Agency Updates</u>		
CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH	Information	CDC and <i>ex officio</i> members
8:45 Influenza		
· Introduction		Dr. Ruth Karron (ACIP, WG Chair)
· Influenza surveillance update		Dr. Lisa Grohskopf (CDC/NCIRD)
· Update on effectiveness of live-attenuated and inactivated seasonal influenza vaccines in children and adolescents	Information & Discussion	Dr. Brendan Flannery (CDC/NCIRD)
· Administering Afluria® Influenza Vaccine via PharmaJet® Stratis® Needle-Free Injection		Dr. Charles Altman (bioCSL)
10:05 Vaccine Supply	Information	Dr. Jeanne Santoli (CDC/NCIRD)
10:20 Break		
10:50 Novel Influenza		
· Introduction		Dr. Jon Temte (ACIP, WG Member)
· Influenza A (H5N1) epidemiology and vaccine	Information & Discussion	Dr. Sonja J. Olsen (CDC/NCIRD)
· GRADE and policy options for influenza A (H5N1) vaccine		Dr. Sonja J. Olsen (CDC/NCIRD)
11:50 Pertussis		
· Introduction	Information & Discussion	Dr. Art Reingold (ACIP, WG Chair)
· Health-care personnel and Tdap vaccination		Dr. Jennifer Liang (CDC/NCIRD)
12:50 Lunch		
2:05 General Recommendations		
· Introduction	Information &	Dr. Marietta Vázquez (ACIP, WG Chair)

	· Timing and spacing; contraindications and precautions; vaccine administration	Discussion <u>Vote</u>	Dr. Andrew Kroger (CDC/NCIRD)
3:10	Child/Adolescent Immunization Schedule		
	· Introduction	Information & Discussion <u>Vote</u>	Dr. José Romero (ACIP, WG Chair)
	· Child/Adolescent schedule 2015		Dr. Raymond Strikas (CDC/NCIRD)
3:55	Break		
4:15	Adult Immunization Schedule	Information & Discussion <u>Vote</u>	
	· Introduction		Dr. Laura Riley (ACIP, WG Member)
	· Adult immunization schedule 2015		Dr. David Kim (CDC/NCIRD)
4:45	Hepatitis		
	· Introduction		Dr. Arthur Reingold (ACIP, WG Chair)
	· Update on hepatitis A disease burden and hepatitis A population protection	Information & Discussion	Dr. Noele Nelson (CDC/NCHHSTP)
5:30	Public Comment		
5:45	<u>Adjourn</u>		
<u>Thursday, October 30th</u>			
8:00	Unfinished Business		Dr. Jonathan Temte (Chair, ACIP)
8:15	Meningococcal Vaccines		
	· Introduction		Dr. Lorry Rubin (ACIP, WG Chair)
	· 4CMenB serogroup B meningococcal vaccine		Mr. Jim Wassil (Novartis)
	· rLP2086 serogroup B meningococcal vaccine	Information & Discussion	Dr. Laura York (Pfizer)
	· Epidemiology of serogroup B disease in the United States		Ms. Jessica MacNeil (CDC/NCIRD)
	· Considerations for use of serogroup B meningococcal vaccines in the US		Dr. Manisha Patel (CDC/NCIRD)
	Public Comment - meningococcal vaccines		
10:00	Typhoid Vaccines	Information & Discussion <u>Vote</u>	
	· Introduction		Dr. Barbara Mahon (CDC/NCEZID)
	· Typhoid vaccines update		Dr. Brendan Jackson (CDC/NCEZID)
10:30	Vaccine Safety		
	· Proposed changes to the Vaccine Adverse Event Reporting System (VAERS) reporting form	Information & Discussion	Dr. Tom Shimabukuro (CDC/NCEZID)
10:45	Break		

11:00 **Human Papillomavirus (HPV) Vaccines**

- | | | |
|---|-------------------------------------|--|
| <ul style="list-style-type: none"> · Introduction · Program summary and new 9-valent HPV vaccine trial data · Cost effectiveness Cost effectiveness of 9-valent HPV vaccination · GRADE for 9-valent HPV vaccine · Policy options and discussion | <p>Information & Discussion</p> | <ul style="list-style-type: none"> Dr. Joseph Bocchini (ACIP, WG Chair) Dr. Alain Luxembourg (Merck) Dr. Marc Brisson (Laval University, Quebec, Canada) Dr. Emiko Petrosky (CDC/NCHHSTP) Dr. Lauri Markowitz (CDC/NCHHSTP) |
|---|-------------------------------------|--|

1:00 **Public Comment****1:15** **Adjourn*****Acronyms***

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DOD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	CDC National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
Tdap	Tetanus, Diphtheria, and acellular Pertussis Vaccine
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Events
AFP	American Family Physicians
AIS	Adenocarcinoma in Situ
AMA	American Medical Association
ANA	American Nurses Association
APHIS	Animal and Plant Health Inspection Service
ARI	Acute Respiratory Infection
ASH	Assistant Secretary for Health (HHS)
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
DHS	Department of Homeland Security
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Acellular Pertussis Vaccine
DVA	Department of Veterans Affairs
ED	Emergency Department
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
EOC	Emergency Operations Center
EPSDT	Early and Periodic Screening, Diagnostic and Treatment
FDA	Food and Drug Administration
fHbp	Factor H Binding Protein
FLU VE	Influenza Vaccine Effectiveness Network
GIE-STFM	Group on Immunization Education – Society for Teachers of Family Medicine
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GRWG	General Recommendations Work Group
GSK	GlaxoSmithKline
HA	Hemagglutinin
HAV	Hepatitis A Vaccine
HBIG	Hepatitis B Immune Globulin
HCP	Healthcare Personnel
HCUP	Healthcare Utilization Project
HCV	Hepatitis C Virus
HHS	(Department of) Health and Human Services

Hib	<i>Haemophilus influenzae</i> Type b
HICPAC	Healthcare Infection Control Practices Advisory Committee
HIV	Human Immunodeficiency Virus
HPAI	Highly Pathogenic Avian Influenza
HP2020	Healthy People 2020
HPV	Human Papillomavirus
HR	Hazard Ratio
HRSA	Health Resources and Services Administration
hSBA	Human Serum Bactericidal Assay
IAC	Immunization Action Coalition
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IM	Intramuscularly
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IRAT	Influenza Risk Assessment Tool
ISO	Immunization Safety Office
ISTF	Immunization Safety Task Force
IVS	Institute for Vaccine Safety
JIFI	Jet Injection for Influenza
LAIV	Live Attenuated Influenza Vaccine
LTBI	Latent Tuberculosis Infection
MATS	Meningococcal Antigen Typing System
MCRF	Marshfield Clinic Research Foundation
MCV4	Meningococcal Conjugate Vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
NACI	National Advisory Committee on Immunization, Canada
NadA	Neisserial Adhesin A
NAPNAP	National Association of Pediatric Nurse Practitioners
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCVIA	National Childhood Vaccine Injury Act
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHBA	Neisseria Heparin Binding Antigen
NHIS	National Health Interview Survey
NGOs	Non-Governmental Organizations
NIH	National Institutes of Health
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNII	National Network for Immunization Information
NNV	Number Needed to Vaccinate
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVICP	National Vaccine Injury Compensation Program
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NYC DOHMH	New York City Department of Health and Mental Hygiene

OB/GYN	Obstetrician/Gynecologist
OHCS	Office of Health Communication Science
OMV	Outer Membrane Vesicles
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PPE	Personal Protective Equipment
PI	Principal Investigator
PPSV	Pneumococcal Polysaccharide Vaccine
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
QALYs	Quality Adjusted Life Years
QI	Quality Improvement
RCT	Randomized Controlled Trial
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SAHM	Society for Adolescent Health and Medicine
SBA	Serum Bactericidal Assay
SCC	Squamous Cell Carcinoma
SME	Subject Matter Expert
Td	Tetanus-Diphtheria
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Inactivated Vaccine
UAMS	University of Arkansas for Medical Sciences
UCHealth	University of Colorado Health
UCLA	University of Southern California, Los Angeles
UK	United Kingdom
UPMC	University of Pittsburgh Medical Center
US	United States
USC	University of Southern California
USDA	US Department of Agriculture
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine Effectiveness
VEC	Vaccine Education Center
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
ViCPS	Vi capsular polysaccharide
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particles
VRBPAC	Vaccine and Related Biologic Products Advisory Committee
VRC	Vaccination Report Card
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization

Welcome and Introductions

Welcome

Dr. Larry Pickering Executive Secretary, ACIP / CDC

Following Dr. Temte's greeting and call to order, Dr. Pickering welcomed everyone to the October 2014 Advisory Committee on Immunization Practices (ACIP) meeting. He indicated that the proceedings of this meeting would be available to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. He then recognized several others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Stephanie Thomas, Natalie Greene, Reed Walton, and Chris Caraway.

Emphasizing that there would be a full agenda for both days of the meeting, Dr. Pickering noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within 90 days following this meeting. Meeting minutes are posted on the ACIP website generally within 90 days of the meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Jamila Howard Jones or Jason McDonald for assistance in arranging interviews.

Dr. Pickering welcomed the following international guests in attendance:

- Dr. Aisha Mohammed Alshammary, Manager, National Immunization Program for the Ministry of Health, Saudi Arabia
- Dr. Hsiu-Yun Lo, Section Chief, Division of Acute Infectious Diseases, Centers for Disease Control, Taiwan
- Dr. Yu Min Chou, Deputy Director, Division of Acute Infectious Diseases Centers for Disease Control, Taiwan

As a reminder for future international visitors to ACIP meetings, due to changes in Department of Homeland Security (DHS) Policy, additional forms will be required for each meeting at the time an international guest registers. It is critical that international visitors complete and submit these forms as soon as possible following registration. Stephanie Thomas, Committee Management Specialist, will be able to help with any questions and concerns about the process. The next ACIP meeting will convene at CDC on Wednesday and Thursday, February 25-26, 2015. Registration for all meeting attendees is required and will be open Friday, October 31, 2014. The registration deadline for United States (US) citizens is Monday, February 9, and for non-US citizens is Monday, February 2. Registration is not required for webcast viewing.

Dr. Pickering offered the following notes regarding members and liaison representatives:

Members

- Kathy Harriman and Doug Campos-Outcalt are unable to join the meeting.

Liaisons

- Tami Thomas attended this meeting on behalf of Patsy Stinchfield, representing the National Association of Pediatric Nurse Practitioners (NAPNAP).
- Chad Rittle will be replacing Katie Brewer as the American Nurses' Association (ANA) liaison.
- Ian Gemmill will be replacing Bryna Warshawsky as the National Advisory Committee on Immunization (NACI), Canada.
- The Healthcare Infection Control Practices Advisory Committee (HICPAC) has withdrawn as a liaison organization to ACIP.

To avoid disruptions during the meeting, Dr. Pickering requested that those present turn off all cell phones. He explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. Time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before any votes. Those who planned to make public comments were instructed to visit the registration desk in the rear of the auditorium to have Stephanie Thomas record their name and provide information about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

This is the 50-year anniversary of ACIP, which held its first meeting in May 1964 in a building that no longer exists. Dr. Frieden joined the October 2014 meeting for a few moments to commemorate this notable anniversary. An article titled, "History and Evolution of the Advisory Committee on Immunization Practices — United States, 1964–2014" was published on October 24, 2014 in the *Morbidity and Mortality Weekly Report (MMWR)* [63(42); 955-958]. A longer article titled, "History of the United States Advisory Committee on Immunization Practices" will be published in the journal *Vaccine*.

Safety issues will continue to be presented during every ACIP meeting. A separate vaccine safety presentation was planned for the second day of the October 2014 meeting.

With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those specific vaccines. However, they are

prohibited from participating in committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in a discussion with a proviso that he or she abstains on all votes related to the vaccines of that company. It is important to note that at each meeting, ACIP members state any conflicts of interest.

Applications for ACIP membership are due no later than November 14, 2014 for the 4-year term beginning July 2015. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

E-mail: acip@cdc.gov Web homepage: <http://www.cdc.gov/vaccines/acip/index.html>

Nominations: <http://www.cdc.gov/vaccines/acip/committee/req-nominate.html>

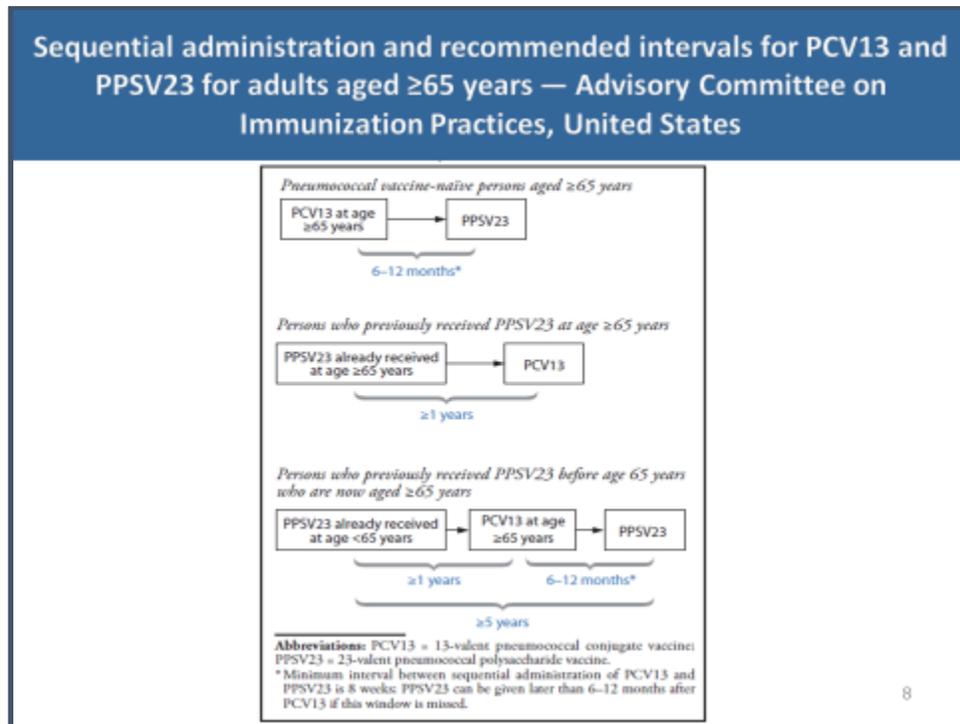
A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submitted as e-mail attachments to Stephanie Thomas at hkp4@cdc.gov

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, reaffirmed, or retired. Links to these recommendations and schedules can be found on the ACIP website. A listing of recommendations that have been published since the June 2014 ACIP meeting follows:

ACIP Recommendations Published Since June 2014		
Title	Publication Date	MMWR Reference
<ul style="list-style-type: none"> Use of MenACWY-CRM Vaccine in Children Aged 2 Through 23 Months at Increased Risk for Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices 	6/20/2014	2014;63(24):527-530
<ul style="list-style-type: none"> Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014–15 Influenza Season 	8/15/2014	2014;63(32):691-697
<ul style="list-style-type: none"> Human Papillomavirus Vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP) 	8/29/2014	2014;63(RR05):1-30
<ul style="list-style-type: none"> Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Recommendations of the Advisory Committee on Immunization Practices (ACIP) 	9/19/2014	2014;63(37):822-825

<http://www.cdc.gov/vaccines/hcp/acip-recs/recs-by-date.html>

The following algorithm designed by the Pneumococcal Vaccines Work Group (WG) illustrates the pneumococcal conjugate vaccine (PCV)13 and PCV23 recommendation made during the August 2014 ACIP meeting for adults aged ≥ 65 years of age:



The following resource information pertaining to ACIP is available on the CDC website:

Vaccine Safety:

www.cdc.gov/vaccinesafety/index.html

Immunization Schedules (2014):

<http://www.cdc.gov/vaccines/schedules/index.html>

Vaccine Toolkit:

<http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html>

Immunization for Women (American College of Obstetricians and Gynecologists):

www.immunizationforwomen.org

You Are the Key to HPV Cancer Prevention:

<http://www.cdc.gov/vaccines/youarethekey>

Vaccines for Preteens and Teens:

<http://www.cdc.gov/vaccines/who/teens/index.html>

Dr. Pickering announced that friend, colleague, and former ACIP member, Dr. Mike Marcy, died on September 5, 2014 following a very short battle with cancer. At the time of his death, Dr. Marcy was a Clinical Professor of Pediatrics at both University of Southern California (USC) and University of Southern California, Los Angeles (UCLA). He served on the ACIP from July 1, 2008 to June 30, 2012. Committee chairs during his tenure were Drs. Dale Morse and Carol Baker.



While a member of ACIP, Dr. Marcy was chair of the Pneumococcal WG and a member of the Human Papillomavirus (HPV) and Meningococcal WGs. He was nationally and internationally recognized in the field of pediatric infectious diseases, was a member of the American Academy of Pediatrics (AAP) Red Book Committee, and a recipient of many national awards. Dr. Marcy was a unique ACIP member in that he arrived in Atlanta one to two days before each meeting to read all of the extensive information provided to members before each meeting. In addition, during meetings, the discussions in which he was involved were always very stimulating. Dr. Marcy is survived by his beloved wife, Joan, and their two adult children, Stephanie and Josh, and by all who knew him well. We are all sorry that he is gone, but happy for what he has left us. Thank you, Mike.

Before officially beginning the meeting, Dr. Temte called the roll to determine whether any ACIP members had conflicts of interest. The following conflicts of interest were declared:

- Belongia: Receives research funding from MedImmune
- Bennett, Bocchini, Harrison, Karron, Jenkins, Kempe, Pellegrini, Reingold, Riley, Romero, Rubin, Temte, and Vazquez: No conflicts

Dr. Temte extended an expression of gratitude to all of the staff at CDC who have been working non-stop over the last several months in terms of the response to the Ebola outbreak in West Africa. A number of subject matters experts (SMEs) who typically assist ACIP have been deployed either domestically or internationally to help in this effort. The number of hours these folks are putting in agency-wide is unimaginable.

This marks the 50th anniversary of the ACIP, as Dr. Pickering noted. The *MMWR* publication, "History and Evolution of the Advisory Committee on Immunization Practices — United States, 1964–2014" published on October 24, 2014 was authored by Drs. Jean Smith, Alan Hinman, and Larry Pickering. Dr. Temte took this opportunity to talk about the Who, What, When, Where, and Why of ACIP. He began with an introduction of the three new members:



Ed Belongia, MD

Dr. Belongia is the Senior Epidemiologist/Director of the Epidemiology Research Center at Marshfield Clinic Research Foundation (MCRF) in Marshfield, Wisconsin. Dr. Belongia is an internationally recognized expert in the epidemiology of infectious diseases, vaccine safety and effectiveness, and antimicrobial resistance. He has also been a Principal Investigator (PI) for the Vaccine Safety Datalink (VSD) for Marshfield Clinic, and has worked extensively with the Influenza Vaccine Effectiveness (Flu VE) Network.



Laura Riley, MD

Dr. Riley is the Director of Labor and Delivery and Obstetrics and Gynecology Infectious Disease at Massachusetts General Hospital in Boston, Massachusetts. Her interests are in human immunodeficiency virus (HIV) disease in pregnancy, infectious disease complications of pregnancy, medical complications of pregnancy, and high-risk pregnancy. She was previously the liaison to ACIP for the American College of Obstetricians and Gynecologists (ACOG), and is the first Obstetrician/Gynecologist (OB/GYN) to serve on ACIP, pointing to the increased number of issues related to vaccination during pregnancy.



Jose Romero, MD

Dr. Romero is a Professor in the College of Medicine and Department of Pediatrics, the Section Chief of Infectious Diseases, and a Horace C. Cabe Endowed Chair in Pediatric Infectious Diseases at the University of Arkansas for Medical Sciences (UAMS) in Little Rock, Arkansas. Dr. Romero has served on the Food and Drug Administration's (FDA's) Vaccine and Related Biologic Products Advisory Committee (VRBPAC), and is interested in healthcare delivery and research among underrepresented minority communities. He has extensive expertise in molecular virology, pediatric infectious disease, and vaccine science.

The following is the first ACIP meeting agenda. The topics included influenza, pertussis, smallpox, measles, and rubella:

First ACIP Meeting: May 25-26, 1964

Agenda

Surgeon General's Advisory Committee on Immunization Practices
Room 327
Communicable Disease Center
May 25-26, 1964

Monday, May 25 - 9:00

1. Introduction - Committee purpose and function Dr. Goddard
2. Previous Immunization Advisory Committees Dr. Langmuir
3. Definition of committee responsibility Dr. Goddard
 - a. Relationship to "Red Book" Committee
 - b. Relationship to other committees on immunization, e.g. APHA, NCHD, etc.
4. Simplification of immunization schedules Dr. Weil
5. Influenza
 - a. Influenza, 1963-1964, national and international Dr. Silverman
 - b. Influenza strains Dr. Anderson
 - c. Vaccine use - 1963 Dr. Anderson
 - d. Field studies of vaccine efficacy - 1963-64 Dr. Anderson
 - e. Vaccine composition Dr. Murray
 - f. Blood group antibodies induced by vaccine Dr. Anderson
 - g. Recommendations - 1964-65
 - (1) Feasibility of outbreak
 - (2) Recommendations for vaccine use
 - (3) Recommendations regarding field studies

Tuesday, May 26 - 9:00

6. Rubella
 - a. Status report - probability of vaccine Dr. Murray
 - b. Disease etiology in prophylaxis Drs. Murray & Anderson
 - c. Recommendation regarding immune globulin in prophylaxis
7. Rubella
 - a. Status report - vaccine use Dr. Anderson
 - b. Immunization schedules employing killed and live vaccines Dr. Chiese
 - c. Recommendations regarding use of combined killed and live vaccines

- 2 -

8. Smallpox
 - a. Status report - vaccine use Dr. Henderson
 - b. Complications of vaccination Dr. Miller
 - c. Smallpox control in the U.S. Dr. Langmuir
 - d. Changes proposed by the World Health Organization in the International Vaccination requirements
9. Simultaneous administration of live vaccines Drs. Anderson & Murray
10. Concluding discussion

Communicable Disease Center

Taken from the Charter [www.cdc.gov/vaccines/acip/committee/charter.html], ACIP's role is to provide guidance:

"... regarding the most appropriate selection of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population.

... on population groups and/or circumstances in which a vaccine or related agent is recommended.

... on contraindications and precautions for use of the vaccine and related agents and provides information on recognized adverse events.

... deliberations on use of vaccines to control disease in the U.S. shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, economic analyses and implementation issues.

... periodically review and, as appropriate, revise a list of vaccines for administration to children and adolescents eligible to receive vaccines through the Vaccines for Children Program.”

Dr. Temte shared a humorous video about herding cats to illustrate the work of ACIP, which can be found at the following link:

https://search.yahoo.com/search;_ylt=AoJhOPi6FiUg7CH_e0ZLYzKbvZx4?p=herding+cats+video&toggle=1&cop=mss&ei=UTF-8&fr=yfp-t-302&fp=1

The first ACIP meetings were convened in Room 207, Building 1 of CDC. The room was so small that it would not have accommodated the current members. ACIP meets three times a year in February, June, and October. Sometimes special meetings are convened to address specific issues, such as the meeting in August 2014 to vote on PCV13 and PCV23. The August 2014 meeting was conducted via teleconference and included over 1200 attendees. The following table indicates the number of cases of disease prevented for the cohort of children between 1994 and 2013, a 20-year time frame. During that timeframe, 322 estimated illnesses, 21 million hospitalizations, and 731 premature deaths due to vaccine-preventable illnesses were averted in this cohort:

Vaccine-preventable disease*	Cases prevented (in thousands)		
	Illnesses	Hospitalizations	Deaths
Diphtheria	5,073	5,073	507.3
Tetanus	3	3	0.5
Pertussis	54,406	2,697	20.3
<i>Haemophilus influenzae</i> type B	361	334	13.7
Polio	1,244	530	14.8
Measles	70,748	8,877	57.3
Mumps	42,704	1,361	0.2
Rubella	36,540	134	0.3
Congenital rubella syndrome	12	17	1.3
Hepatitis B	4,007	623	59.7
Varicella	68,445	176	1.2
Pneumococcus-related diseases†	26,578	903	55.0
Rotavirus	11,968	327	0.1
Total	322,089	21,055	731.7

CDC. Benefits from Immunization During the Vaccines for Children Program Era — United States, 1994–2013. MMWR 2014; 63(16):352-5.

Dr. Temte shared a clip from Laura Huber, the mother of twins, in which she describes the autopsy of her son Abe who died at 5 months of age from pertussis. She concludes by saying, “The worst part is I think he got it from me.” This clip can be found at the following link:

http://www.youtube.com/watch?v=2_CdlAg9FH0. He also shared this quote, “It wasn’t just the pain of their loss that tormented them. It was that the love for their children was still in them, and it had nowhere to go...” from Neely Tucker [Love in the Driest Season, 2004]. Since the inception of ACIP, the world has witnessed the global eradication of smallpox, measles elimination in the US, and the verge of global polio eradication.

Dr. Frieden's Welcoming Remarks

Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

Dr. Frieden thanked the ACIP for all that it does. ACIP is a wonderful example of what the public health community aspires to, which is ensuring that decisions are made based on data, openly and objectively derived, in a public process, and having that information be widely adopted throughout the country to save lives. He welcomed the three new ACIP members, Drs. Belongia, Riley, and Romero and thanked them for dedicating their time and efforts to this process.

This is the 50th year of ACIP. Last week, CDC published an *MMWR* detailing the history of ACIP. Much has changed in that 50-year period. There are many new vaccines, with an increase from 6 to 16 childhood and adolescent vaccines and a total of 15 adult vaccines. During his first ACIP meeting as Director, Dr. Frieden teased one of the members that ACIP is turning our children into pin cushions will all of these vaccines, and the member replied, "No, we're doing that to adults also." Yet, there is still so much further to go in terms of closing the gaps between vaccine recommendations and vaccine delivery, and in developing new vaccines that are even more effective against more disease and that will protect more children and adults and will save more lives. ACIP will continue to be central to that process.

A lot of progress has been made. Influenza season is upon us, and thought is being given to the importance of influenza and pneumococcal pneumonia vaccines and how important those are. Consideration is also being given to connectivity, because it is known controlling disease within one population protects other populations as well. Disease rates decrease generally when childhood vaccination rates are increased. As vaccination against influenza is increased, the hope is that this will be observed with influenza as well. The pneumonia vaccination recommendations are complicated and they are new, but they are important because pneumonia and pneumococcal disease are important to fight. Of course, PCV13 is still included in the standard childhood vaccine schedule and pneumococcal polysaccharide vaccine (PPSV) 23 is recommended for children at higher risk as well.

Public health is a best-buy. Vaccines are a great demonstration of that best-buy. In working to stop Ebola in West Africans and to protect Americans in the US, careful consideration is being given to two vaccine candidates. In the near future, it is hoped that these two vaccines will undergo randomized trials—one a standard RCT and the other a step-wedged design that CDC may be leading. This is important because vaccines are very powerful weapons. It is important to determine where vaccination can play a role in disease control anywhere it might be possible. This is yet another reminder of how critically important vaccines are to health, and what a strong tool they are for disease control.

In conclusion, Dr. Frieden thanked the ACIP members for all of the work they do, for saving lives, and for keeping children and adults healthy. Ultimately, the roles of ACIP and CDC are to rigorously assess what the science shows; openly state what is known and what is not known; set the best possible policy based on the best possible science; and support all partners in state and local health departments, hospitals, health centers, communities, and patient advocacy

groups to get the best possible recommendations implemented and information provided to patients and doctors in order to protect as many lives as possible. He also encouraged those who had not received their influenza vaccine to get it.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat reported that the National Influenza Vaccination Week events will be December 7-13, 2014. This offers an opportunity to promote late-season vaccination. CDC plans to convene its Immunization Information Systems (IIS) Metrics Blue Ribbon Panel to help define metrics for success for the future priorities the agency plans to implement. The Ebola response is currently CDC's highest priority, and most CDC staff are involved in this effort. The agency is working with others across the US government and partners in West Africa, industry, and other countries to try to accelerate vaccine evaluation and potential availability for Ebola. The epidemic's evolution is such that vaccines may be needed to control it. CDC's primary role at this point is working on a step-wedged vaccine design plan to be implemented in Sierra Leone and possibly additional locations. The agency has a team in Sierra Leone working with their counterparts in the government, as well as the United Kingdom (UK), to flesh out plans for that. Simultaneously, the National Institutes of Health (NIH) has efforts underway to develop a randomized controlled trial (RCT) for implementation in Liberia. Dr. Schuchat recently attended a World Health Organization (WHO) meeting that assembled the stakeholders and those who are keen to make progress as rapidly as possible. The focus of the work that CDC is developing would be the target of vaccine evaluation for the healthcare personnel (HCP) and other frontline caregivers in Sierra Leone. Beginning October 1, 2014, Dr. Nancy Messonnier became the Deputy Director of the National Center for Immunization and Respiratory Diseases (NCIRD). Dr. Messonnier is known for her expertise in bacterial meningitis, pertussis, and infectious disease prevention and response. She will be working closely with everyone in the immunization effort.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance reported that the Centers for Medicare and Medicaid Services (CMS) is in the process of updating and clarifying Medicare coverage of pneumococcal vaccines given the recent ACIP recommendations using an expedited process. CMS anticipates having more information to share during the February 2015 ACIP meeting. In addition, CMS has worked with the National Vaccine Program Office (NVPO) again this year to release weekly information on influenza cases in Medicare. The FluView map and Flu Trends data are available on the NVPO website.

Department of Defense (DoD)

Dr. Geibe reported that there have been no new Department of Defense (DoD) immunization policies since the last ACIP meeting, other than an update on annual influenza guidance. The DoD goal is 90% for service members by 15 December 2014. That is expected to be reached, as it was last year. Although Dr. Geibe will remain involved with the ACIP, there will be a DoD replacement representative for the next ACIP meeting. He also announced that the Ebola responders would be receiving their influenza vaccinations that day in the Emergency Operations Center (EOC).

Department of Veteran's Affairs (DVA)

Dr. Kinsinger announced that the Department of Veteran's Affairs (DVA) launched its VA Retail Immunization Care Coordination Program in September 2014. This retail partnership is with Walgreens. Information about certain vaccines given by Walgreens pharmacists to VA-eligible Veterans will be sent electronically to their VA medical record, and will be viewable by their VA providers in the regular place where all immunizations are recorded. For this year, information about influenza, pneumococcal, and zoster vaccines will be transmitted to recipients' VA electronic medical records (EMR). The VA is funding about 75,000 influenza vaccines for Veterans enrolled in the VA for healthcare. All Walgreen stores throughout the country are participating. Other retail pharmacies will be added as the program is expanded. The VA is working to update its clinical guidance and electronic decision support tool, called Clinical Reminders, for the pneumococcal vaccination to align with the recent ACIP recommendation for PCV13 in older adults. That will be in place in a couple of months. Work is also underway to develop a Clinical Reminder for the Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap), Tetanus-Diphtheria (Td), and zoster vaccines. Week 42 influenza activity is low across the VA, as it is across the country based on number of hospitalizations, influenza-like illness (ILI) visits, testing, and positive laboratory results. Since August, approximately 900,000 doses of vaccine have been administered to Veterans in the VA healthcare system.

Food and Drug Administration (FDA)

Dr. Sun reported that the FDA has prioritized review of the two meningococcal B vaccines manufactured by Pfizer and Novartis. Those reviews are ongoing, with a regulatory action anticipated soon. The FDA is also involved in the Ebola outbreak response working with CDC, NIH, and other regulatory agencies to implement human testing with available vaccines. There have been two noteworthy approvals since the last ACIP meeting. The first was the approval of AFLURIA[®], to be given by the PharmaJet[®] needle-free injection system. This approval was based on an immunogenicity non-inferiority study in approximately 1200 subjects 18 through 65 years of age with a 1:1 randomization. The second was the approval of Menactra[®] for use as a booster for ages 15 through 55. This was evaluated as an open-label study among 834 subjects 11 years of age and older who received their last dose 4 to 6 years previously.

Health Resources and Services Administration (HRSA)

Dr. Houston indicated that the Advisory Commission on Childhood Vaccines (ACCV) has made recommendations to amend the Vaccine Injury Table on several dates, the latest being September 5, 2014. These recommendations are based on the Institute of Medicine's (IOM) review of the scientific literature on vaccines and adverse events. These recommendations are being considered by the agency. Increasing numbers of petitions are being filed by the National Vaccine Injury Compensation Program (NVICP) each year. The highest number of claims filed with the program occurred during fiscal year 2014, which was 611. Increasing numbers of claims are also being compensated. In fiscal year 2013, 351 claims were compensated and in fiscal year 2014, 365 claims were compensated. Over \$200 million were paid in compensation to petitioners. The NVICP, which compensates individuals and families of individuals who have been injured by vaccines, which is a rare event, is an alternate to the traditional tort system. The Health Resources and Services Administration (HRSA) has instituted an outreach campaign in order to inform people that this is a safety net that is available to them in the event that they are injured by vaccines. HRSA will reach out to partners in order to promote awareness of the program.

Indian Health Services (IHS)

Ms. Groom reported that the Indian Health Service (IHS) has begun an aggressive influenza campaign. IHS also has developed a new Influenza Vaccination Action Plan to align with the goals of the Healthy People 2020 (HP2020) that includes a number of strategies, including performance measures to help IHS achieve that goal. IHS has administered 184,000 doses of influenza vaccine to date in its patient population. IHS is also rolling out its Hepatitis B Clinical Reminder for people with diabetes mellitus, which was to go live in the next week, and is working with the VA on the PCV13 Clinical Reminder and hope to have that rolled out within a month.

National Institutes of Health (NIH)

Dr. Gorman emphasized NIH's continued interest in antimicrobial resistance, which is tangentially associated with ACIP. Through its Antimicrobial Resistance Leadership Group, NIH is working on stewardship, behavioral changes, development of new antibiotics, and exploration of the role of vaccines in addressing the continued problem of antimicrobial resistance. NIH and CDC are working collaboratively to develop a clinical trial for Coccidioidomycosis (Valley Fever) in the affected areas of California and Phoenix, with implementation anticipated in summer 2015. NIH's hepatitis C virus (HCV) candidate trial continues to enroll well, and results for that trial should be available soon. The agency is soon to go into the clinic with its first broadly protective (alternatively called "universally protective) influenza vaccine. Regarding Ebola, he echoed Dr. Schuchat's observation that "it takes a village to save the world." This is an incredible effort on the part of the US government, other governments, non-governmental organizations (NGOs), HCPs, and the pharmaceutical industry all working together to try to address this situation. Currently, NIH plays a role throughout the entire spectrum of development of agents and is presently evaluating five potential therapeutics and three potential vaccines, and is assessing preclinical targets and testing previously approved medications and medications specifically developed for Ebola to determine whether they may be effective against this agent. Toxicity studies for the vaccines have been accelerated to meet some FDA requirements, and the number of non-human primates in studies have been expanded to acquire better data on potential correlates of protections. System biology is being utilized to assess the differences between the vaccine candidates that protect and those that do not protect non-human primates. Enrollment has been completed for a Phase 1 vaccine trial in the US for one candidate vaccine, and planning is underway for several other potential Phase 1 and Phase 2 trials for different candidates. In terms of the potential efficacy or effectiveness trial, considerations continue regarding the best possible design that is implementable and that will result in data to offer confidence that these vaccines work and are safe and effective.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein announced that the National Vaccine Advisory Committee (NVAC) published a report on enhancing uptake of vaccines recommended for pregnant women, and is now embarking on the second phase to determine how to incentivize development of vaccines intended for pregnant women for existing vaccines with that indication and new vaccines intended for that group. NVAC is also involved in the mid-course review of the National Vaccine Plan (NVP), which is a 10-year plan, and will be working with the National Vaccine Program Office (NVPO) and potentially making recommendations for change. NVAC has two WGs, one which focuses on improvement of HPV vaccine uptake for which recommendations are

anticipated soon, and another that focuses on overcoming vaccine confidence/hesitancy for which preliminary recommendations should be ready for review during the next NVAC meeting.

National Vaccine Program Office (NVPO)

Dr. Gellin reported that the previous week, HHS Secretary Burwell announced the appointment of a new Acting Assistant Secretary for Health (ASH), Dr. Karen B. DeSalvo. She is the National Coordinator for Health Information Technology, an area that does not go unnoticed in immunizations. Before coming to the Department of Health and Human Services (HHS), she was the Health Commissioner in New Orleans and was significantly involved in the rebuilding of the health system there following Hurricane Katrina. With CMS, NVPO published a piece in Medscape that explains the Affordable Care Act (ACA) and immunizations. The piece is intended for providers and includes resources. He also thanked ACIP for having Dr. Frieden introduce the importance of adult immunizations. NVPO is in the process of clearing an adult immunization strategic plan. ACIP will have an opportunity to review and offer input on the draft plan.

Influenza

Introduction

Ruth Karron, MD
Chair, Influenza Work Group

Dr. Karron reported that since June 2014, the Influenza WG has focused primarily on 2013-2014 vaccine effectiveness estimates for live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). They have heard data from the US Flu VE Network, the Armed Forces Health Surveillance Center, and MedImmune on a post-marketing study of quadrivalent LAIV. During this session, updates were presented on influenza surveillance, effectiveness of LAIV and IIV seasonal influenza vaccines in children and adults, administering AFLURIA[®] influenza vaccine with the PharmaJet[®] Stratus[®] needle-free injection device, and the influenza vaccine supply.

Influenza Surveillance Update

Lisa A. Grohskopf, MD, MPH
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

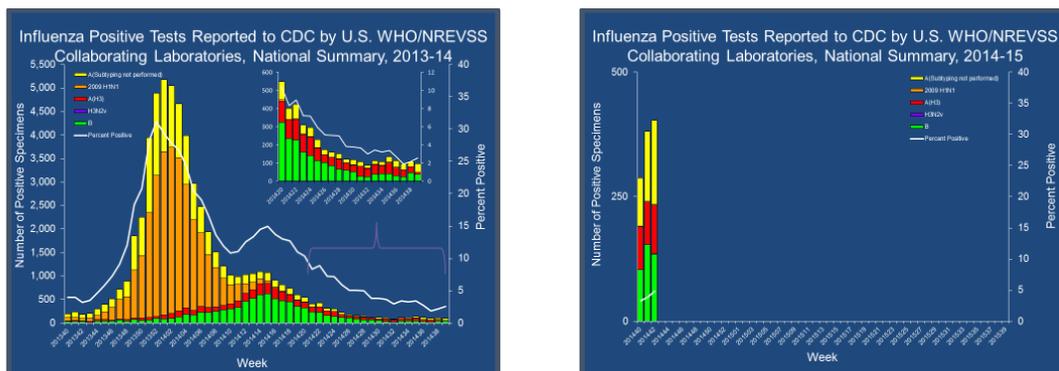
Dr. Grohskopf indicated that during Week 42, widespread influenza activity was reported by Guam. Local influenza activity was reported by Puerto Rico and five states: Alaska, Connecticut, Florida, North Carolina, and Texas. Sporadic influenza activity was reported by the US Virgin Islands and 36 states: Alabama, Arkansas, California, Colorado, Delaware, Georgia, Hawaii, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, New Hampshire, Nebraska, New Jersey, New Mexico, New York, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, South Dakota, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming. No influenza

activity was reported by the District of Columbia and nine states: Arizona, Idaho, Illinois, Kansas, Missouri, Montana, Nevada, Rhode Island, and Tennessee.

Based on FluSurv-NET data for laboratory-confirmed influenza hospitalizations by age reported to the system during the period October 1, 2013 to April 30, 2014, the highest rates of hospitalization were observed among people aged 65 and older. In the previous season, 2012-2013, the next highest rates were observed among the very youngest in the US population, those zero through 4 years of age. Neither of these is atypical. Last season, the next highest rates of hospitalization were observed in middle-aged adults, those aged 50 through 64 years of age. In terms of the proportion of hospitalizations contributed from each age group, the 2013-2014 season was the first H1N1 predominant season since the pandemic of 2009-2010. It is interesting to note that the portion of hospitalization contributed by adults 19 through 64 years of age was 57%, which is the highest in that age group since the pandemic.

There has been one pediatric death report thus far the 2014-2015 season. For the 2013-2014 season, a total of 109 pediatric deaths were reported to CDC. Among the isolates for which subtyping was performed, 44 Influenza A (2009 H1N1), 6 were Influenza A (H3N2), 38 were Influenza A (subtype not determined), 17 were Influenza B, 2 were Influenza A and B co-infection, and the subtyped was not determined for the remaining 2.

The following graphics depict influenza positive tests reported to CDC by the US WHO National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories for the 2013-2014 compared to the 2014-2015 season:



While 2009 H1N1 predominated the 2013-2014 season, only 1% of H1N1 has been observed thus far in the 2014-2015 season. Only three weeks into the current system, it is far too early to make a statement about what type of season this will be.

Regarding what is being observed specifically with H3N2 viruses, the WHO recommendation for composition of the 2014-2015 Northern Hemisphere vaccines is the same as it was for the 2013-2014 season, A/Texas/50/2012. The Northern Hemisphere recommendations are usually made in February and the Southern Hemisphere recommendations are usually made in September. WHO convened in September to discuss the recommended vaccine composition for the 2015 Southern Hemisphere vaccine. Of note, they recommended a different H3N2 virus, A/Switzerland/9715293/2013 (H3N2)-like virus, for the upcoming Southern Hemisphere 2015 vaccine. Dr. Grohskopf briefly reviewed some of the data upon which this recommendation was based. Antigenic characteristics of H3N2 viruses collected from February through August 2014 were assessed using panels of post-infection antisera, including hemagglutinin (HA) inhibition

and virus neutralization assays. Many isolates were still well-inhibited by antisera raised against the cell-propagated reference viruses A/Texas/50/2012 and A/Victoria/361/2011; that is, they were similar to the viruses included in the 2013-2014 and 2014-2015 Northern Hemisphere seasonal vaccines. However, an increasing proportion were poorly inhibited by these antisera, and antisera raised against egg-propagated A/Texas/50/2012. On that basis, the 2015 Southern Hemisphere H3N2 is an A/Switzerland/9715293/2013 (H3N2)-like virus. Based on this information from surveillance, antigenic drift is anticipated among H3N2 viruses in the Northern Hemisphere for the 2014-2015 season.

Discussion Points

Acknowledging that it is early in the season, Dr. Reingold asked whether the vaccine strains are a reasonable match for the H3N2 strains being observed.

Dr. Grohskopf replied that antigenic characterization data for the isolates seen thus far this season would probably not be available for another three to four weeks. In terms of antigenic characterization for the 2013-2014 season, the overall match was pretty good.

Based on previous experience, Dr. Temte asked how predictive the first few weeks are in terms of the distribution of H3N1 viruses.

Dr. Grohskopf responded that it is difficult to make generalizable statements across seasons. Last season, a fair amount of H1N1 was observed early and that did persist. There was a later uptick in B, but not near the prevalence of H1N1.

Update on Effectiveness of LAIV and IIV Inactivated Seasonal Influenza Vaccines in Children and Adults

Brendan Flannery, PhD
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Flannery reminded everyone that the US Flu VE Network provides estimates of seasonal influenza vaccine effectiveness against circulating influenza viruses each season. In past seasons, the US Flu VE Network has presented to ACIP interim estimates of vaccine effectiveness during the season as well as end-of-season estimates. The US Flu Vaccine Effectiveness Network is a cooperative agreement between CDC and the following five sites within the US.

- University of Michigan and Henry Ford Health System
- University of Pittsburgh Schools of the Health Sciences and University of Pittsburgh Medical Center (UPMC)
- Baylor Scott and White Health, Texas A&M University Health Science Center College of Medicine
- Group Health Research Institute
- Marshfield Clinic Research Foundation

LAIV use within the network has been increasing, which has allowed the opportunity to evaluate effectiveness by vaccine type. The objectives of this presentation were to compare the effectiveness of LAIV and IIV vaccines among children and adolescents during three influenza seasons (2011-2012, 2012-2013, and 2013-2014); and summarize other data from observational studies that evaluated LAIV and IIV effectiveness among children and adolescents during the 2013-2014 influenza season.

As a review of the methods used by the US Flu VE Network, participating sites enroll outpatients aged 6 months and older who present with acute respiratory illness and cough within 7 days of symptom onset. This is a prospective case-control study that uses a test-negative design. All enrolled outpatients are tested for influenza by reverse transcription polymerase chain reaction (RT-PCR). Cases are outpatients with confirmed influenza, while controls are outpatients who test negative for influenza. Vaccination status is confirmed by medical record or immunization registry data. Only those considered fully vaccinated per the ACIP recommendations 14 or more days before illness onset are included. Vaccine effectiveness (VE) is calculated as $1 - \text{adjusted odds ratio} \times 100$. Estimates are adjusted for age, sex, study site, days from illness onset to enrollment, high risk health status, calendar time, race and ethnicity, and parental-rated general health status. The analysis presented by Dr. Flannery included only enrollees ages 2 through 18 years of age who received only one type of vaccine in a season. He presented VE of LAIV versus unvaccinated children, VE of IIV versus unvaccinated children, and the relative effectiveness of LAIV to IIV which directly compares these two groups.

Since the pandemic H1N1 virus emerged in 2009, it has continued to circulate as a seasonal virus, although at varying amounts each season. Last season had the largest number of H1N1 viruses since the 2009 pandemic. Based on the number of influenza positive subjects of all ages by type/subtype enrolled in the US Flu VE Network for the past 3 influenza seasons, cases due to the 2009 H1N1 pandemic virus were identified in each of the 3 seasons but contributed a small proportion of all cases in 2011-2012 and 2012-2013 seasons.

In terms of the total number of influenza-positive cases included in the analysis and the number of cases vaccinated with LAIV, in the first two seasons, the adjusted VE estimates were high and had largely overlapping confidence intervals. In 2013-2014, the VE estimate was not statistically significant. When the data were stratified by age group (2 through 8 years of age and 9 through 18 years of age) low VE was seen for the 2013-2014 season in the younger age group. The adjusted VE of IIV against any influenza was high and statistically significant for all seasons included in this analysis. Unlike LAIV, a VE estimate was observed in 2013-2014 that was similar to those from previous seasons. When stratified by age group, similar estimates were found.

In a side-by-side comparison of LAIV and IIV against no vaccine for 2 through 18 years old by influenza type and subtype, for the H1N1pdm09 virus for the three seasons combined, very low effectiveness was observed for LAIV against the pandemic H1N1 virus, moderate IIV effectiveness was seen against the pandemic H1N1 virus, there was a slightly lower overall significant effectiveness for H3N2 for IIV and a very similar point estimate for LAIV, and there was moderate effectiveness for B strains that was similar for LAIV and IIV. A similar pattern is observed among 2 through 8 year olds, with low effectiveness of LAIV over those three seasons against the H1N1 pandemic strain and similar effectiveness for both vaccines for H3N2 and B strains.

For the analysis of the relative effectiveness of LAIV compared to IIV, an odds ratio less than 1 indicates superior effectiveness of LAIV, an odds ratio greater than one indicates superior effectiveness of IIV, and that 1 indicates no difference in effectiveness between vaccine types. During the 2011-2012 and 2012-2013 seasons, VE of LAIV and IIV were equivalent among 2 through 18 year olds, with confidence intervals that include one. In 2013-2014, IIV had higher relative effectiveness than LAIV and the difference was statistically significant. When stratified by age group, for children 2 through 8 years of age, point estimates indicated higher relative effectiveness of LAIV compared to IIV in 2011-2012 and 2012-2013, although differences were not significant, with confidence intervals including 1. However, in 2013-2014, the relative effectiveness of IIV was higher than LAIV and statistically significant. LAIV and IIV effectiveness was equivalent for all three seasons among the older children and adolescents.

Analyses of US Flu VE Network data are subject to several limitations. It is not possible to disentangle single season versus pandemic H1N1-specific effects since there was low circulation of the 2009 pandemic H1N1 virus in the study populations in the seasons preceding the 2013-2014 season. The ability to measure age-group specific VE by vaccine type in the US Flu VE Network depends both on vaccine uptake and sample size. In the analyses presented during this session, there was limited ability to control for potential confounding variables due to small sample sizes.

In summary, during the 2011-2012 and 2012-2013 influenza seasons, relative effectiveness favored LAIV versus IIV in young children but was not statistically significant. During the 2013-2014 season, relative effectiveness favored IIV versus LAIV in young children. H1N1pdm09 was the predominating virus for the first time during the 2013-2014 season. The subtype-specific analysis is consistent with poor VE for LAIV against this virus. However, a specific issue related to the 2013-2014 season cannot be ruled out such as an issue with the study enrollees or design, unmeasured confounding, or a vaccine issue. For that reason, CDC asked the manufacturer and the DoD to review their data for LAIV effectiveness. The data from both were presented to the Influenza WG, and Dr. Flannery presented a review of the available data from the 2013-2014 season on LAIV and IIV effectiveness in children and adolescents from MedImmune and the DoD.

MedImmune study results are similar to CDC results based on data from a post-licensure effectiveness study MedImmune is conducting. This is the first season of that study. However, LAIV effectiveness was observed for influenza B. There was not enough B in the US Flu VE Network to make an estimate specifically for influenza B for LAIV that was significant. MedImmune found no significant effectiveness for A/H1N1 pandemic virus overall. They found significant differences in effectiveness observed by vaccine lot shipping time, but have no clear explanation for that at present. Comprehensive investigations into potential explanations are ongoing. They do believe that there are differences by lot that might be explained by H1N1 strain potency loss. A/California LAIV is more susceptible to thermal degradation due to a unique HA stalk sequence, and those results have been published [Cotter et al, PLoS Pathogens, 2014]. The sequence is not present in seasonal influenza LAIV strains, which were used for the clinical trials of IIV versus LAIV.

The MedImmune Study of LAIV effectiveness includes community-dwelling children 2 through 17 years of age in the following US locations:

- Vanderbilt/Tennessee
- Wake Forest/North Carolina
- Scott and White/Texas
- Marshfield Clinic/Wisconsin

Two of these sites are from the US Flu VE Network, but the children are not recruited from the same clinic so there is no overlap with the data presented from the US Flu VE Network study. MedImmune used a similar test-negative design, with RT-PCR confirmed influenza, medically attended acute respiratory illness with onset <5 days, and a vaccination history confirmed by medical record or registry. The study excludes children vaccinated <14 days before their visit. The MedImmune data shared by Dr. Flannery were based on the 1033 subjects included in this analysis.

While there were overlapping confidence intervals in these data, there was a suggestion of lower effectiveness for LAIV. Broken down by subtype, it is clear that there was a difference in the point estimates for the H1N1 in LAIV versus IIV. For B the estimates are similar and high for both vaccines. In the analysis being conducted to assess the week that a lot was shipped, weeks when the lots may have been exposed to high temperatures that could have affected the lots were assessed (e.g., Weeks 4 through 9 or early August through mid-September). These are the weeks during which high temperatures could have affected the lots, specifically in terms of the potency of the H1N1 2009 vaccine virus. MedImmune found no effectiveness for the children who received those lots of vaccines versus a pretty reasonable effectiveness estimate for early or later shipments. The same effect was not observed in the US Flu VE Network data analyzed with the same information regarding the date of shipping lots.

Dr. Flannery also presented data from the DoD's influenza vaccine effectiveness study in Air Force children 2 through 17 years of age for the 2013-2014 influenza season. This study was limited to Air Force dependents, given that it is the only service that has a database of immunizations for all dependents. They also used a test-negative design; however, they included both PCR+ and culture-confirmed influenza versus PCR-negative controls. Their test-negatives are essentially all PCR-confirmed negative, even though they used PCR or culture. The analysis controlled for month of diagnosis, confirmed vaccine history from Air Force immunization tracking, included those who received vaccine >14 days prior to lab test, and adjusted for up to a 5-year vaccination history. DoD found moderate VE for any vaccine type and significant VE for IIV for all age groups. No VE was shown for LAIV for any age group. They believe that the low LAIV VE may be related to the predominance of A/H1 circulation this season. They did not have a large enough sample size to have significant VE when analyzed by subtype, but the subtype analysis is very consistent with no or low VE for the pandemic H1N1 2009 strain.

In conclusion of all of the observational data presented during this session for the three US studies conducted during the 2013-2014 season, all used a test-negative design and all reported low VE for LAIV4. All three studies reported higher and significant VE for IIV among the same groups of children and adolescents. All three studies reported low VE for LAIV4 against H1N1pdm09 in 2013-2014. The MedImmune post-licensure study reported significant VE for LAIV4 similar to IIV against influenza B-Yamagata, but not for H1N1pdm09.

Grading of Recommendation Assessment, Development and Evaluation (GRADE) of LAIV

Lisa A. Grohskopf, MD, MPH
Influenza Division
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Centers for Disease Control and Prevention

In the interest of putting this information in the context of recent decisions voted upon in June 2014 related to LAIV and IIV for children, Dr. Grohskopf presented some summary observations. Prior to the current season, healthy children 2 through 8 years of age would have been recommended to receive either LAIV or IIV with no specific preference recommended for either vaccine. Leading up to the June 2014 ACIP meeting, there was discussion of several studies that suggested potential advantages of LAIV over IIV, including better vaccine efficacy and better heterotypic protection against drifted strains. Several countries (Canada, the UK, Israel, Germany) and two US states (Washington, Oregon) previously expressed some degree of LAIV preference for young children. The age ranges and specific details of the populations to which the preference applies vary, but some form of language was expressed by these jurisdictions. In June 2014, ACIP recommended that LAIV should be used when available for healthy children aged 2 through 8 years, following a Grading of Recommendation Assessment, Development and Evaluation (GRADE) assessment of data from two comparative RCTs.

The GRADE assessment was presented during the June 2014 ACIP meeting, with numerous outcomes discussed. The most relevant outcome for this particular conversation is laboratory-confirmed influenza, which was valued as a critical outcome for policy decision-making. The data evaluated for this outcome are from two RCTs, Belshe¹ and Ashkenazi², which were both comparative studies of LAIV and IIV. One arm was included for each of these vaccines. Overall, the pooled relative risk ratio was 0.46 with a confidence interval of 0.39% to 0.54% favoring LAIV for providing increased protection relative to IIV against laboratory-confirmed influenza. For this analysis, it is important to remember that the influenza cases included all influenza types and subtypes (all A(H1N1), A(H3N2), and B) without regard to antigenic similarity to viruses in vaccine during that given season [¹Belshe et al, NEJM 367;7: 685-696; ²Ashkenazi et al, PIDJ 2006;25:870-879].

To the extent that it was reported in the Belshe and Ashkenazi manuscripts, type-specific information was assessed. Belshe (2007) was conducted for the 2004-2005 season. This was a randomized, placebo-blinded comparative trial of LAIV and IIV. For example, if a child received LAIV they received a placebo for IIV. Because no children received only placebo, it is not possible to assess absolute VE from this study. Only relative LAIV as compared to IIV could be evaluated. All H1N1s that season were antigenically matched to the vaccine, which that season included A/New Caledonia/20/1999. As this study was conducted over the 2004-2005 season, it was pre-pandemic, so the 2009 H1N1 was not yet in the mix for circulation or vaccine. Relative VE for LAIV versus IIV specifically for H1N1 was 89.2% and had a significant confidence interval of 67.7% to 97.4%. All H3N2 were antigenically mismatched compared to the vaccine—all were drifted. Nevertheless, the relative VE for LAIV versus IIV was 79.2% with a significant confidence interval of 70.6% to 85.7%. B viruses from both lineages were circulating and were represented in the samples from that study. Some matched vaccine and some did not. Relative VE for the matched strains was 27.3%, but the confidence interval was not significant at -4.8% to 49.9%. Relative VE for the mismatched was 6.3%, again with a

confidence interval that was not significant at -31.6% to 33.3% [Belshe et al, NEJM 367;7: 685-696].

Ashkenazi (2006) was conducted for the 2002-2003 season. This was a randomized, open-label comparative trial of LAIV versus IIV with no placebos given. The authors note in the paper that cases included A(H1N1), A(H3N2), and B viruses regarded as antigenically similar to vaccine, as well as some H3N2 cases that were regarded as antigenically distinct from vaccine. The vaccine A(H1N1) was the same as the Belshe study, A/New Caledonia/20/1999. Again, this was a pre-pandemic study. Results specific to the mismatched strains alone are not reported. They are mainly relevant for H3N2. For type/subtype-specific A(H3N2), without regard to match, the relative VE of LAIV versus IIV was -47.9% with a very wide confidence interval of -236.5% to 32.6%. This is difficult to interpret, and is probably due to the small numbers in the sample [Ashkenazi et al, PIDJ 2006;25:870-879].

To summarize, comparative studies of LAIV and IIV were conducted prior to 2009 pandemic. There are no H1N1pdm09-specific efficacy data available from RCTs, and there is relatively little effectiveness data for monovalent LAIV that was administered during the pandemic. 2013-2014 was the first H1N1-predominant influenza season since 2009 pandemic. The data presented during this session provide what is believed to be the first clear indication of suboptimal effectiveness of LAIV for H1N1pdm09 virus. Ongoing investigation is in progress, given that the explanation for the 2013-2014 findings is not known. As alluded to by Dr. Flannery in his presentation, differences by lot shipping time in the MedImmune data are currently under investigation. Good VE for LAIV against influenza B has been observed, with similar findings for H1N1 in three different datasets. Therefore, it is not clear whether there is a specific handling issue since that would be expected to impact influenza B as well. Current data are from observational studies, so there is a potential for biases or residual confounding. However, somewhat similar findings seen in three different datasets at this point strengthens the observations.

As noted in Dr. Flannery's presentation, LAIV H1N1pdm09 may be less stable and more subject to thermal degradation than seasonal H1N1 LAIV viruses have been [Cotter et al, 2014]. The sequence in HA stalk confers higher susceptibility to thermal degradation. It is conceivable that this potentially could affect stability and/or the replicative fitness of the vaccine virus. This is a live virus vaccine, so in order to work, it does need to multiply in the nasal mucosa. That would be a potentially biologically plausible explanation, and could also be consistent with previous good VE observed with seasonal H1N1 strains and 2013-2014 observations of good effectiveness of LAIV against influenza B isolates.

Looking forward, the 2014-2015 vaccine has already been produced. No changes are anticipated this season. The US Flu VE Network is receiving additional resources to increase enrollment of children, and this issue will continue to be evaluated. The WG will continue to discuss additional data from these and other sources as it becomes available.

Discussion Points

Dr. Karron emphasized that the "Silver Lining" in identification of a problem with the H1N1 component of LAIV was due to the strong VE network and information from DoD. This problem may not have been recognized this quickly 5 to 10 years ago. Regarding early circulation of A strains and prediction of what will circulate during the season, she wondered if would be a fair

statement, based on the VE network data, to say that generally one A strain predominates and the A strain that is identified early in the season tends to be the predominant strain.

Dr. Flannery replied that in the season that followed the pandemic, there was similar circulation of the pandemic H1N1 and H3N2 viruses. That is uncommon and that analysis was able to give subtype-specific estimates for VE. If there is co-circulation of both A subtypes this season, it would add to the data on this phenomenon and would allow for comparison of the H3 and H1 VE for those two vaccines for the same season. In most seasons, one A strain seems to be dominant and the subtype-specific analysis does not make sense until some seasons are combined.

Dr. Reingold asked whether the stalk issue pertains only to H1N1 or is also an H3N2 issue. In addition, he said that while he understands the issues of observational studies and confounding, he is not personally persuaded that confounding and uncontrolled confounding is the issue here. He did not see how it could pertain to the effectiveness estimates for H1N1 and not for B.

Dr. Grohskopf responded that it appears that the issue is specific to the sequence that confers that particular vulnerability with the H1N1pdm09 virus. Her understanding is that this was observed in the wild type 2009 pandemic viruses early in the pandemic, but that there since has been some evolution away from that and the current wild type viruses are more stable. This does not appear to be an issue with seasonal H1N1 or H3N2 viruses.

In terms of moving forward, Dr. Harrison inquired as to whether there are ways to assess the current lots that have been produced and avoid the issue of problematic lots from last year.

Dr. Grohskopf replied that more information is anticipated from the DoD prior to the February ACIP meeting. The US Flu VE Network will also continue to collect data. In regard to moving forward and the vaccine, the vaccine has been produced for this season. She requested that a representative from MedImmune comment on that.

Regarding replacement of the 2009 pandemic H1N1 component with a more stable virus, Dr. Karron noted that a paper published earlier in the year discussed a more stable, later isolated variant.

Kathleen Coelingh (MedImmune) responded that this is an odd immunoassay sequence in the stalk region in the pandemic strain. The exact copy was used and was introduced into MedImmune's vaccine because that was the sequence they were supposed to use for the vaccine. Currently, the strains have lost that particular change. So, MedImmune is very interested in making a change in its vaccine for the 2015-2016 season if the strain does not change. They would get an antigenically similar strain to the 2009 H1N1 California strain, which does not contain the mutation that is undesirable in the stalk. That would be one of the more recent strains. It would be an update.

Dr. Karron asked whether MedImmune has thoughts about ways to assess the thermostability or infectivity that would help decide whether the replacement strain is better than the one currently in the vaccine.

Kathleen Coelingh (MedImmune) responded that they do.

Dr. Kempe expressed confusion about whether the lot issue is really the problem. She asked whether it was possible to assess the different lots in other datasets such as the Air Force data to determine whether there was variability between different lots.

Dr. Flannery replied that he did not have the data for the Air Force by lot, and he did not believe they assessed this. The US Flu VE Network analyzed the same way for lot does not show this.

Dr. Romero asked whether data could be obtained from countries in the Southern Hemisphere regarding the effectiveness of LAIV.

Dr. Grohskopf responded that she did not know the prevalence of LAIV in the Southern Hemisphere, and welcomed comments about that from MedImmune. It is licensed in Canada, the UK, Germany, and Israel. However, in many of those countries it has been licensed only recently. The US has had it since 2003, but Canada and the UK use has been relatively recent.

Kathleen Coelingh (MedImmune) added that the vaccine is not currently licensed in any of the Southern Hemisphere countries.

Dr. Temte asked whether in the usual approach, illness severity was assessed in people who presented with acute respiratory infection (ARI) and cough. He also wondered how rapidly the annual VE estimates could be calculated once the season is over.

Dr. Flannery indicated that there have been a couple of attempts in the US Flu VE Network to assess scores that are essentially cumulative numbers of symptoms and self-described severity of illness by ambulatory patients. Those scores have not differentiated very well in terms of evaluating differences in VE. Dr. Belongia's group has performed some of those assessments. In terms of when data will be available for this season, in retrospect, it would have been possible to assess effectiveness for the 2013-2014 season earlier had interim data been used. This is typically not used for vaccine-specific VE in order to wait for documentation and verification. However, self-report is quite good for LAIV versus IIV types of comparisons. Therefore, it should be possible to provide interim estimates to help update the analysis presented during this session. Again, it will depend upon what circulates this season.

Dr. Belongia added that differences have not been observed in severity; however, the universe of people in the study are those who have presented to see a physician. People who stay home are not captured. There has been some methods work on this that suggests that the study design being used is, under reasonable assumptions, probably a valid measure of VE for preventing influenza illness, not just for preventing medically attended influenza. In terms of the other severity issue, in general, approximately 80% to 90% of people with influenza meet the ILI criteria even though that is not required to be in the study. Only cough is required.

Dr. Schuchat mentioned that for some years, CDC also supported VE evaluation against hospitalized, laboratory-confirmed influenza through the Emerging Infection Program (EIP) network. After a couple of years, the conclusion was made that there was comparable VE for hospitalization and medically attended illness, and that it was more cost-effective to use the outpatient system for estimates of VE and the EIP network for estimates of disease burden. This is believed to be a reasonable approach for the more and less severe ends of the spectrum.

Regarding the data presented, Dr. Michael Decker (Sanofi Pasteur) pointed out that there have been publications on LAIV and IIV suggesting that one's response to vaccination depends in part upon prior exposure to influenza vaccine. He wondered whether the VE network has collected information regarding prior influenza vaccination exposure, or might do so in the future.

Dr. Flannery replied that this is one of the questions raised by Dr. Reingold about potential confounders not being very convincing. However, it is difficult to separate out the group that received LAIV from the sites that have relatively high vaccination rates. He shared a table showing the LAIV recipients for various age groups in 2013-2014 compared with the receipt of vaccine in 2012-2013. Not shown is the LAIV group in 2013-2014 that was unvaccinated in 2012-2013 because there are so few of them. Almost all LAIV recipients had received either LAIV or IIV in the previous season, and several had received vaccines over several seasons. The take-home message is that the percentage of influenza positives looks very similar for LAIV recipients no matter what they received in the previous season, but the numbers are very small. That is the issue with potential confounding. It looks lower in the IIV group for this season, and most of those received IIV in the previous season. In terms of the number of cases left out, there were only 34 LAIV recipients total. Only a few LAIV recipients either received two doses, with their first season in 2013-2014, or received one dose but had not received a vaccination in the previous season. Prior vaccine is being assessed as an explanation, but the age-specific findings are not understood. It may be that they are not so age-specific, but is just something related to sample size and the populations being studied.

Dr. Decker (Sanofi Pasteur) said that while those were interesting data, that was not the question he was asking. ACIP recommended LAIV preferentially for persons from 2 through 8 years of age—not the entire population because there is evidence that as people age and have more experience with influenza, the differential benefit of LAIV disappears perhaps because of sufficient antibody. The question regards whether improved vaccination of the pediatric population in the last decade since those randomized studies were conducted changed the environment such that LAIV is no longer as beneficial in young people as it used to be, because they have now had several doses of vaccine before the age at which LAIV is indicated.

Dr. Flannery said he understood the question, and if “you have a hammer, everything still looks like a nail.” He would still probably use this same slide to answer the question. There is limited ability to assess the effects of several years of prior vaccination on take of vaccine, whether it is by type or by any vaccination. That is an area of great interest and a lot of work in the US Flu VE Network. It is difficult to do that with observational data. It would also be difficult to design a trial to assess that question. It does seem that prior vaccination or prior infection changes the response not only to LAIV, but also to IIV. He would argue that the data seen in the 2013-2014 season in the US Flu VE Network challenges that idea because both the younger and older children had received several vaccinations. The older group might have had more natural infections during the pandemic. It suggests that the older group, and maybe some in the younger group, received some benefit of vaccination. It perhaps elicited their immune response, their memory response, to that particular antigen. Even though the younger group had been vaccinated, there appeared to be less response to the LAIV. That is the group who, if they had a low baseline, would be expected to respond better to LAIVs. The answer is that this is still not understood, but it is an area of active research.

Regarding Dr. Flannery's Slide 14 with 95% confidence intervals over three seasons for H3N2, Dr. Kimberlin (AAP) asked whether LAIV was not statistically significantly affected.

Dr. Flannery responded that there is slight overlap with no effectiveness. H3N2 estimates over three seasons are complicated by whether the same vaccine virus is in the vaccine and what is circulating. There was confidence in doing that for these three seasons for H1N1 because there was very little antigenic change in what was circulating, and very little antigenic change in the virus. Multiple year analyses have been performed for H3 effectiveness, but as Dr. Grohskopf presented, for trials all influenzas are used and match is broken down by antigenic match and mismatch of the vaccine. Those are mixed in this analysis, so the three-season analysis was not meant to make a comparison of LAIV to IIV for the H3N2 subtype. It could certainly be said that there are issues with both vaccines in terms of the effectiveness of the H3N2s for the younger group.

Dr. Karron requested that Dr. Flannery show these data for 2 through 8 year olds, noting that while the distributions are somewhat different, the point still holds.

Dr. Plotkin (Vaccine Consultant) pointed out that the stability problem was reported by MedImmune in January 2014, meaning that they knew it well before that time. That suggests that the standard stability tests that are done for licensure should have shown a problem with the H1N1 strain. MedImmune might have data anticipating what happened. For the future, everyone believes in LAIV for young children based on prior studies. Those studies were of a live vaccine that induced both serum antibody and mucosal antibody. He suggested that for the coming seasons, the study of immune responses should be repeated because there is no magic involved in this. If those same responses can be shown, it would indicate that the problem in the last year will not be repeated, so it is crucial. MedImmune should have retrieved material that that was sent out this season to titer it, because it is a live virus. Therefore, it can be determined whether the vaccine is still potent by titrating the materials that were stored.

Dr. Christopher Ambrose (MedImmune) affirmed that Dr. Plotkin was correct about this mutation being known. It was in the pandemic 2009 A/California strain, which is why it is in MedImmune's vaccine strain. The monitoring of the stability of the 2013 vaccine, like all years, is done. Several lots are monitored for stability and potency over time. That is stored in 2 to 8 degrees Celsius without any deviations from the recommended storage of the vaccine. No stability problems were observed with any of the monitored lots of the H1N1 vaccine strain. The data published in the paper show that potentially, exposures to higher than 2 to 8 degrees Celsius that could occur during distribution, may have an impact. MedImmune does not have knowledge that this did occur, but is investigating whether that could have happened during the warmest or hottest weeks of the year when the vaccine is being loaded or offloaded. MedImmune is in the process of working with its distributors to assess potency of distributed vaccine for this year. All of the available data have been confirmed, and there is no evidence of any breaks in the cold chain this year or problems with potency.

Dr. Schaffner (NFID) commented that if this is a stem stability problem, he remained confused about the age effect and the postulated lot effect. He was also curious about the FDA's role in this.

Dr. Sun (FDA) indicated that the FDA had a discussion with CDC about these data, and has also undergone some internal investigations to evaluate the immunogenicity of vaccines through the FDA's evaluation process. Because there are so many potential variables at this point, the FDA is still in the investigational stage. Further discussion with MedImmune may be needed, but this is currently a work in process.

Dr. Grohskopf noted that one of the ideas discussed regards whether it might be a vulnerability settling effect that would not necessarily manifest itself on a standard stability assay, but would perhaps have some effect on the replicative fitness of the virus. That might not be inconsistent with an observed difference in age because efficacy of any influenza vaccine by age is known to be variable for many reasons. Some other unknown factor might be interacting.

Dr. Temte recapped that ACIP would be interested in assessments of lot potency; monitoring the strains likely to be in circulation this year, which will affect performance of the vaccine and ACIP's recommendations; and early availability of interim VE estimates from the US Flu VE Network in terms of future planning.

Administering AFLURIA[®] Influenza Vaccine Via PharmaJet[®] Stratus[®] Needle-Free Injection

**Charles (Chip) Altman, MD, MBA
US Head, Medical Affairs
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Dr. Altman reminded everyone that the FDA recently approved AFLURIA[®] for use in a new needle-free delivery system. While this delivery system is not for every patient, it is an important option. Trypanophobia is the fear of needles that applies to children and adults. Recently published surveys show that about one quarter of all adults fear needles. It is estimated that 7% of adults avoid immunizations due to fear of needles. Some very prominent people fear needles, including a talk show host, a former heavy weight boxing champion, and a famous karate stunt man. Needle fear is taken very seriously, given that it is a barrier to immunization.

The fear of needles is a barrier not only for the patients, but also for the people administering the vaccines. Annually, there are approximately 800,000 needle-stick injuries in the US and 3.5 million worldwide. There are also fiscal and psychological burdens, with \$2 billion in burden in the US alone. The cost of needle-stick testing/counseling is approximately \$3,000. The cost of needle-stick treatment ranges from \$3,000 to \$100,000. Needle-sticks transmit many blood-borne diseases; however, needles are reused 40% to 70% in the developing world [International Health Care Worker Safety Center, Needlestick and Sharps Injury Prevention Act, American Journal of Industrial Medicine].

It might be good to avoid the use of needles in certain settings such as the workplace. In Dr. Altman's workplace, a cart is wheeled around to administer influenza vaccine to employees. There really is not a great way to dispose of sharps, so the idea of being able to deliver influenza vaccination without needles is an important option. That is why bioCLS partnered with a very innovative device company in Colorado, PharmaJet[®]. PharmaJet[®] developed a Stratus[®] needle-free injection system. Jet injection systems for administering vaccines are not new. They have existed for about 100 years. During World War II, many immunizations were given by jet injection, some well-received and some not so well-received. The new and improved

system developed by PharmaJet® to deliver AFLURIA® influenza vaccine has an invisible, narrow, precise fluid stream that penetrates skin and enters the deltoid muscle in approximately 0.1 second. The injector has a small single use cartridge at the end of it that injects the thin fluid stream to the proper depth. There is no needle involved in the entire process. The multi-dose vial of AFLURIA® that is used with needle and syringe can also be used with this PharmaJet® system. In many states, the cartridges can be discarded using non-sharps containers because there are no needles. The amount of time it takes to use the jet injector is comparable to using a standard needle and syringe.

The RCT conducted to receive FDA approval was known as the Jet Injection for Influenza (JIFI) study. JIFI was an RCT clinical trial conducted at the University of Colorado Health (UCHealth) system to demonstrate non-inferiority of jet injection versus needle and syringe for administration of AFLURIA® trivalent inactivated vaccine (TIV) influenza vaccine. The study recruited 1250 healthy adults 18 through 65 years of age. This study was published in *The Lancet* in May 2014. The primary objective of the study was to evaluate the non-inferiority of AFLURIA® influenza vaccine administered intramuscularly (IM) by jet injection using PharmaJet® Stratis®. AFLURIA® was administered IM by needle and syringe in healthy adults based on serum hemagglutination inhibition reciprocal titers. Given that this study was conducted in 2012-2013, the prevalent Northern Hemisphere strains used included A/H1N1 (A/California/7/2009), A/H3N2 (A/Victoria/361/2011), and B (B/Hubei-Wujiagang). The secondary objectives were to compare the safety and tolerability of the vaccine administered by PharmaJet® Stratis® or needle and syringe based on specifically solicited local and systemic reactions through 7 days post-vaccination, and adverse events spontaneously reported through day 28 post-vaccination. The study was randomized but not blinded, so patients knew if they received a jet injection or needle and syringe. However, the people evaluating safety and immunogenicity were blinded.

There were six co-primary endpoints, which included the geometric mean titer (GMT) titers and the seroconversion rates for each of the three strains. Criteria were set up in advance of the study for non-inferiority. The GMT ratio had to be ≤ 1.5 at 28 days and the seroconversion rate differences could not exceed 10% to show non-inferiority [Based on Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007]. Secondary safety endpoints included immediate reactions in the 30-minute observation period, solicited local and systemic adverse events (AEs) through the diary cards, and unsolicited AEs and serious adverse events (SAEs) up to and including 28 days after vaccination. Exploratory immunogenicity endpoints included seroprotection and geometric mean fold rise (GMFR). Exploratory patient experience questions were also asked to assess whether patients liked the jet injection and would take it again.

The demographics of the study participants in both arms were comparable by age, sex, and race. The GMTs were nearly identical for jet injection versus needle and syringe, showing that AFLURIA® administered by jet injection results in the same immune response as administering AFLURIA® by needle and syringe at Day 28 post-injection. The overall rate of seroconversion was comparable in both groups, with nearly identical percentages for jet injection versus needle and syringe. The criteria were met for non-inferiority on the GMT ratio and the seroconversion rate. Regarding secondary endpoints, GMFR and seroprotection were also comparable in both groups. Overall, very little difference was observed in AFLURIA® administered by jet injection or by needle and syringe.

More jet injection subjects complained of immediately occurring local symptoms or signs, but the rates were similar between the two groups at later time points. There was a higher frequency of low-grade local reactions with jet injection, but all were low grade. Systemic adverse events were comparable between groups. Of the subjects, 3 experienced 6 SAEs. There was 1 SAE in the jet injection group and there were 2 in the needle and syringe group. All were deemed to be unrelated to the study drug and injection procedure as judged by the clinical investigator. In terms of the patient vaccination experience, subjects were interviewed immediately post-immunization. They were asked, "Would you chose to receive this type of injection again?" Of those who received jet injection, 89% indicated that they would receive it again for their next immunization. More post-marketing surveys have been conducted asking this question since that time, one of which was at the University of Tennessee (UT). Of those surveyed, 80% to 90% have said that they would get the jet injection again despite some of the early complaints that are mild and resolve quickly.

In conclusion, needle fears and needle stick injuries are barriers to influenza immunization. AFLURIA[®] TIV influenza vaccine delivered by PharmaJet[®] Stratis[®] needle-free jet injector met non-inferiority criteria for immunogenicity versus needle and syringe. Local injection-site reactions were reported more frequently in the PharmaJet[®] Stratis[®] injector group, but all were mild to moderate. Systemic AEs were comparable between AFLURIA[®] given with needle and syringe and the jet injector. Post-marketing surveys support patient and health care provider satisfaction with needle-free influenza immunization. The overall goal is to support increased influenza immunization coverage.

Discussion Points

Dr. Reingold recalled working with the Ped-O-Jet in West Africa with which vaccines could be administered to large numbers of people without a needle. One of the concerns with Ped-O-Jets and Med-E-Jet had to do with the machine not being perpendicular to the skin, in which case blood could be produced through some sort of sheering or cutting phenomenon. There were problems with blood contamination of the port. He noted that Dr. Altman presented no data regarding what is known about blood contamination around the needle-free syringe, or what is known about transmission of blood-borne viruses.

Dr. Altman said his understanding was that the small disposable cartridge is what makes the difference. It is about an inch long. The entire cartridge that is used to fill up from the multi-dose vial is discarded, so there is a separation between the skin and the actual jet injector. That piece is disposed of and no needle is involved. No problems have been observed with the cartridge piece, and in many states it can be discarded in a non-sharps container.

Dr. Harrison wondered whether subjects were asked which vaccine they would prefer rather than the way the question was asked.

Dr. Altman responded that they did not. Those who received the PharmaJet[®] jet injection were asked, "Would you chose to receive this type of injection again?"

Dr. Harrison stressed that those are very different questions. It sounded like the subjects were not asked preferentially, but were asked only whether they would get this vaccine again in the jet injection.

Regarding the thickness of the adipose tissue in the arm, Dr. Romero asked whether this device would be sufficient to deliver the vaccine to the muscle and not deposit it in the fat tissue in an obese individual. He also observed that for those who do not like shots because it hurts, this does not accomplish much.

Dr. Altman replied that it is a “one-size-fits-all” for adults. This injector was studied only with AFLURIA[®] and only with adults. There have been no stipulations about the size of anyone’s arm or obesity.

Dr. Vazquez said she was also thinking about obese patients and that depth matters. She asked whether there were any data to show that penetration using the jet injector remains the same in different individuals. Depth of penetration may not matter for this vaccine, but thinking ahead for other vaccines, it might make a difference.

Dr. Altman responded that he did not have data on penetration, but in the development of this device, depth was intended to reach the muscle. He requested that someone from PharmaJet[®] offer further information.

Heather Callender-Potters (Co-Chairman, PharmaJet[®]) indicated that the syringe has an auto-disable feature so that it cannot be reused. The end of the orifice touches the skin. When the high velocity of fluid is created that penetrates the skin, for a moment there is an opening in the skin. In theory, there is a split second where tissue, fluid, or blood could be seen because a hole is being created. However, unlike the Ped-O-Jet, there are no laceration issues with the PharmaJet[®] technology. The spring has been modulated to be appropriate to deliver to target tissues. To address that issue, PharmaJet[®] has submitted 510(K) data to FDA’s Center for Devices and Radiological Health (CDRH) that includes gel and tissue studies to demonstrate depth of penetration. PharmaJet[®] has also conducted its own imaging studies, and has studied a variety of other vaccines (IM, subcutaneous, and intradermal). Depth and amount deposited have been assessed in the intradermal evaluations. She believes that PharmaJet[®] engineering has adequately addressed the concept of reaching the target tissue.

Regarding infection control, Dr. Rubin pointed out that the common use part of the device is reused so presumably this is reloaded. Vaccinators may choose to wear or not wear gloves during vaccination. Obviously, they should be performing hand hygiene. He wondered whether there were any recommendations for wiping down the device to decontaminate between patients or between reloading of the device.

Heather Callender-Potters (Co-Chairman, PharmaJet[®]) said they addressed that with the user interface, in that the injector never touches the patient. There is an auto-eject button on the injector so that once an injection has been given, it is never necessary to touch the patient or the single use syringe, and it can be adequately disposed of. PharmaJet[®] has also tested all of the materials in relation to its injector. A number of common disinfectants can be used and there are heavy plastics and titanium-coated steel, so all of the standards required for hygiene and good practice are met.

As the UT representative who was highly involved in the study Dr. Altman mentioned, Dr. Foster (APhA) said they gave over 2000 vaccines in one day to HCP and the PharmaJet[®] was accepted quite well. Approximately 500 (25%) of the vaccinees immediately chose the PharmaJet[®]. He got the needle-free injection himself just to try it out. It is not pain-free, but he did not observe any difference for himself in the jet injection versus needle and syringe.

Dr. Kenneth Schmader (AGS) asked why people over the age of 65 were excluded in the bioCLS study.

Dr. Altman replied that this study was designed with FDA guidance to evaluate adults. While they did not study the older age group in this particular study, he agreed that it would be beneficial to think about in the future.

Dr. Susan Even (ACHA) expressed interest in knowing how fast using the PharmaJet® injector might be, because it seemed like it might be faster than single dose needle and syringe.

Heather Callender-Potters (Co-Chairman, PharmaJet®) indicated that PharmaJet® has conducted a number of time studies and trials, and the needle-free injector is comparable to needle and syringe for one individual. PharmaJet® has participated in a number of mass immunization activities, the needle-free injector has been deemed several times faster. There is a process associated with loading the injector and downloading, but that can be curtailed with some extra help.

Dr. Sandra Fryhofer (AMA/ACP) asked how much the PharmaJet® needle-free injector costs in comparison to standard delivery mechanisms, noting that she was unable to locate any information on the Internet and had not yet received a response from an email she wrote to the company the week before.

Heather Callender-Potters (Co-Chairman, PharmaJet®) replied that the PharmaJet® system compares favorably to needle and syringe delivery. The PharmaJet® device is slightly more expensive than a needle and syringe, but there is generally expense reduction in the sharps disposal because many choose to use no sharps disposal. Treatment cost, liability, and needle-stick testing are not required because there are no risks associated with those issues. PharmaJet® also tends to be efficient in vaccine recovery. The device has been engineered such that there is basically no wastage of vaccine. This is a very compelling delivery method that is highly cost-effective. The injector has been tested for 30,000 cycles and the device is warranted for 20,000 uses. PharmaJet® actually does not know when the device will fail. Depending upon the volume of the user, the device tends to sell for \$250.00 per injector, so it is fractional pennies per delivery. If people are buying large quantities, PharmaJet® simply gives it away. In terms of the retail price of the cartridge, historically cost tends to be about \$1.00 per shot. Needles tend to cost between \$1.08 and \$1.35 depending upon the needle solution that is used, and whether two needles are used to download the vaccine from the vial.

Dr. Gellen (NVPO) asked for a status on PharmaJet® work with other formulations and other manufacturers for increased flexibility in programs in the future.

Heather Callender-Potters (Co-Chairman, PharmaJet®) indicated that PharmaJet® is working broadly with a variety of vaccines in clinical testing with its collaboration partners. PharmaJet® is highly interested in being an effective tool for influenza vaccines. With its partner, bioCSL AFLURIA®, is anticipated to involve more and longer-term cooperation. These details are not generally shared, but PharmaJet® is extremely grateful for all of the support that has been given to them. They have a great relationship with CDC, WHO, and the FDA. She invited anyone interested in speaking with them further to visit them in the back of the room after this session.

Influenza Vaccine Supply Update

Lisa A. Grohskopf, MD, MPH

Influenza Division

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Dr. Grohskopf reported that while distribution for the current season started off more slowly than in many previous seasons over the last 10 years (2004-2005 - 2014-2015), it exceeded last year's rate of distribution in mid-September and is currently at approximately the same level as vaccine distribution in the 2012-2013 season.

At the national level, the current projection for the US market across all manufacturers is 151 million to 156 million doses. This projection exceeds the total doses distributed during the 2013-2014 season of 134.5 million doses. As of 10/17/14, 117.8 million doses of influenza vaccine have been distributed. Overall, this represents approximately 75% of the vaccine anticipated for the season.

Despite early season shipping delays experienced by several US manufacturers (e.g., GSK, MedImmune, and Sanofi Pasteur), manufacturers anticipate that the majority of their influenza vaccine distribution will occur by the end of October, with some providers continuing to receive partial shipments during November.

National level distribution data can be insufficient to characterize distribution at the local level. For example, because the early season shipping delays impacted certain vaccine brands and specific products within brands differently, some providers may be experiencing spot shortages while other providers are not.

Discussion Points

Dr. Bocchini asked whether the Vaccines for Children (VFC) distribution of influenza vaccine was on par with the private sector.

Dr. Bennett said that her understanding from providers in her region was that VFC distribution was limited by the prior month's order, and that there has been an issue this year with respect to large providers acquiring sufficient doses from the VFC.

Dr. Santoli responded that overall, the VFC receives doses equitably with the private sector. State programs play an important role in VFC distribution in terms of how they want to allocate doses to providers. Not every state operates in the same way. Some states determine that some providers might be priority providers because of the patients they serve. Partial shipments are fairly common to get everyone started so that everyone has at least some vaccine, even if there is not enough vaccine to fill entire orders. At the national level, doses are received in a way that is comparable. However, the way each jurisdiction handled their distribution was probably not identical. Depending upon what providers ordered, they may have experienced receipt differently in one jurisdiction versus another.

Vaccine Supply

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Santoli presented updates for pertussis-containing vaccines and adult hepatitis A and B vaccines.

Regarding pertussis-containing vaccines, Sanofi Pasteur has sufficient supplies of Pentacel[®], Daptacel[®], and Adacel[®] (both vials and syringes) vaccines and has removed all allocations of these vaccines. There are currently shipping delays for GSK's Kinrix[®] vaccine (DTaP-IPV vaccine).

Twinrix[®], GSK's combination hepatitis A/B vaccine is currently out of stock in the private market. This vaccine is licensed for use in those 18 years of age and older, so its use in the VFC program is limited. However, adult formulations of Havrix[®] (hepatitis A vaccine) and Engerix B[®] (hepatitis B vaccine) are available in sufficient amounts to meet anticipated demand.

CDC's Vaccine Supply/Shortage Webpage can be found at:
<http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Novel Influenza

Introduction

Jon Temte, MD, MS, PhD
Advisory Committee on Immunization Practices

Dr. Temte indicated that the rationale for a novel influenza recommendation is that there are two FDA-licensed vaccines for the highly pathogenic influenza A (H5N1) virus. There is a need for a recommendation for use during inter-pandemic periods, especially for those who have an increased risk of exposure. ACIP was seen as the most appropriate body to develop recommendations for these vaccines. This WG was formed because the Seasonal Influenza WG has a full workload. The Novel Influenza WG was formed in February 2014, and was charged with developing recommendations for use of influenza A (H5N1) vaccine during inter-pandemic periods. The policy question was, "Should licensed influenza A (H5N1) vaccine be recommended to adults with increased risk of exposure during the inter-pandemic time period?" If so, the exposure must be determined and the recommendation must be defined.

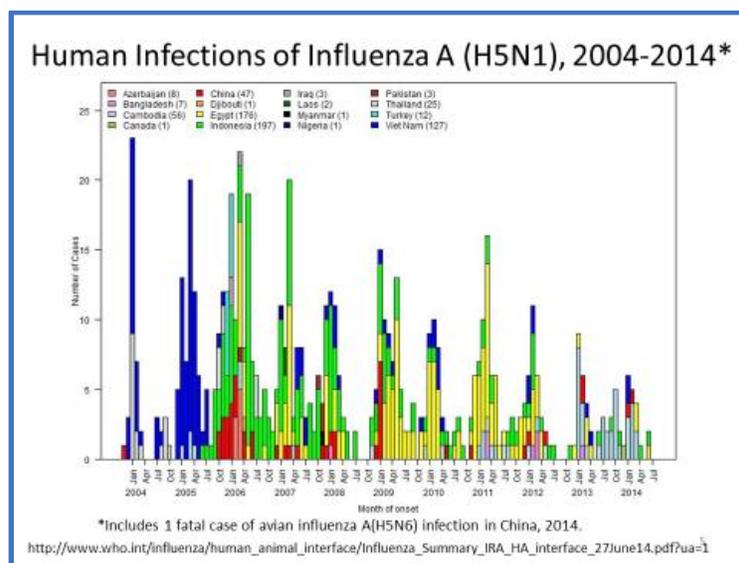
In terms of progress to date, the Novel Influenza WG has been meeting at least monthly and sometimes more frequently. Between February and October Oct 2014, the Novel Influenza WG has met 11 times. This session included presentations from Dr. Sonja Olsen, the CDC Lead for the Novel Influenza WG, on Influenza A (H5N1) epidemiology and vaccine, and GRADE and policy options for influenza A (H5N1) vaccine. The WG anticipates presenting a recommendation for a vote during the February 2015 ACIP.

Influenza A (H5N1) Epidemiology and Vaccine

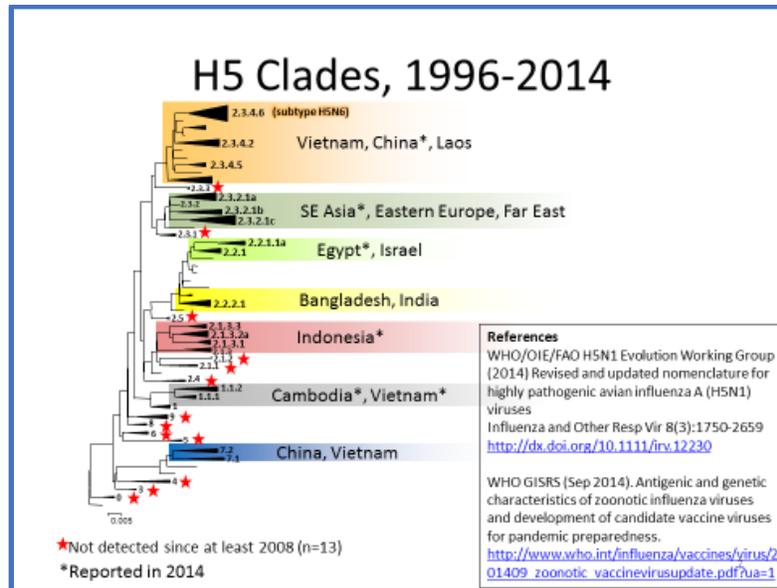
Sonja J. Olsen, PhD

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Olsen reported that influenza A (H5N1) is a highly pathogenic avian influenza (HPAI) virus that causes a highly transmissible, severe respiratory disease in birds. The influenza A (H5N1) virus is endemic in poultry in at least six countries (Bangladesh, China, Egypt, India, Indonesia, and Vietnam), but has also recently been found in Laos and Cambodia. Poultry outbreaks occur frequently in these and neighboring countries. Infections have occurred in humans, the first of which were recognized in Hong Kong in 1997. At that time there were 18 cases in humans, and Hong Kong culled the entire poultry population of approximately 1.5 million chickens. The virus reemerged in Asia in 2003, and the number of infections peaked in 2006. However, every year, including this year, there have been sporadic cases with high mortality. Between 2003 and September 2014, there have been 667 cases in 16 countries. Of these, 393 have died for a mortality of 59%. Most cases occur from close contact with infected live or dead birds, or H5N1 virus-contaminated environments. Human-to-human transmission is extremely rare. In 2014, there were 9 cases in Cambodia, 4 in Egypt, 3 in China, and 2 each in Vietnam and Indonesia. The following depicts the number of cases from each country:



The H5N1 virus continues to evolve. Evolution is monitored using the sequence of the HA gene. Viruses are grouped into clades based on phylogenetic characterization and sequence homology. Knowledge of currently circulating clades and antigenic distance from existing candidate vaccine viruses is relevant to updating pre-pandemic vaccine recommendations. The following shows all H5 clades:



The red stars highlight the 13 clades that have not been detected since 2008. The clades highlighted with colors indicate the countries where that clade has been detected. The asterisks highlight clades and locations where H5 viruses were detected in 2014. For example, Clade 2.1.3, shown in the reddish color, is found in Indonesia and there were viruses detected there this year.

The WHO Strategic Advisory Group of Experts (SAGE) Working Group on Influenza Vaccines and Immunizations has developed global recommendations for use of licensed H5N1 vaccine during inter-pandemic periods. These recommendations were first drafted in 2009 and were reevaluated and reaffirmed in 2013 with no changes. Vaccine is strongly recommended for laboratory workers involved in certain high-risk activities, such as large-scale production with virus. Vaccine is recommended for first responders and health care providers managing patients. Vaccine is not recommended for persons who may only potentially come into contact with infectious animals, workers in areas where the virus is enzootic, and the general population. These recommendations are not specific to any vaccine.

Because H5 viruses continue to evolve, this necessitates frequent development of representative candidate vaccine viruses. WHO recommends that countries consider candidate vaccine viruses for pandemic preparedness purposes based on an assessment of public health risk and needs. Globally, there are currently 26 candidate vaccine viruses in development and 4 in preparation.

In the US, H5N1 vaccines are not made commercially. The US government has supported their development. Candidate vaccine viruses are chosen for vaccine development using a standardized Influenza Risk Assessment Tool (IRAT). Currently, there are four vaccines in the stockpile. The following table shows the four vaccines, highlighting the virus in the vaccine, clade represented, and licensure status:

Virus	Clade	FDA Licensure
A/Vietnam/1203/2004	1	Yes (Sanofi)
A/Indonesia/5/2005	2.1.3.2	Yes (GSK)
A/bar-headed goose/Qinghai/1A/2005	2.2	No
A/Anhui/1/2005	2.3.4	No

Only the first two vaccines are licensed by FDA. Vaccines in the stockpile are for use during a pandemic or for clinical studies of the vaccines. Strain changes are permitted only during an emergency. These vaccines are not meant for use during inter-pandemic times.

One FDA-licensed vaccine (Q-Pan) is being produced post-licensure. The US government supported additional vaccine production post-licensure. The manufacturer is producing one lot of approximately 100,000 doses. It is currently anticipated that this vaccine will be ready in early 2015. A portion of this vaccine will be stored at NIH and made available to investigators, with the rest to be entered into the stockpile.

Q-Pan H5N1 vaccine is made by ID Biomedical Corporation of Quebec, which is a subsidiary of GSK. The vaccine is an emulsion that consists of 3.75µg HA of the influenza virus strain A/Indonesia/05/2005, as well as the AS03_A adjuvant emulsion (full dose, 11.86mg tocopherol). The vaccine is administered intramuscularly in 2 doses 21 days apart. The licensure states that it is approved for use in persons ≥ 18 years of age at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Q-Pan is the first vaccine with AS03 to be licensed in the US. There are no adjuvanted seasonal influenza vaccines licensed in the US. AS03 is an oil-in-water emulsion adjuvant. There are several reasons to use AS03 in influenza vaccines, including increased immunogenicity, antigen dose-sparing, and influenza cross-strain neutralization or an ability to induce an immune response to other strains. AS03 was used in H1N1pdm09 monovalent vaccines, Pandemrix made by GSK in Germany and Arepanrix made by ID Biomedical Corporation in Quebec.

There have been reports of AS03-adjuvanted pH1N1 vaccines associated with narcolepsy. Several studies of Pandemrix, used in many European Union countries, have found an increased risk of narcolepsy in all ages though this is highest in children and adolescents. There have been no studies to date with negative findings. The attributable risk has been as high as 6.25 cases per 100,000 persons vaccinated. In addition, a recently study was released of Arepanrix used in Canada and Brazil. The population-based study in Quebec found a relative risk similar to that observed in European studies of Pandemrix. The attributable risk was lower at 1 case per 1,000,000 doses, but the baseline incidence of narcolepsy was also lower than was found in Europe. Adjuvanted monovalent H1N1pdm09 vaccines were not used in the US. However, because of these findings, CDC sponsored an international study on adjuvanted

H1N1pdm09 vaccines (Arepanrix and MF59-adjuvanted vaccines) and narcolepsy. This study is in progress, with preliminary results expected in late 2015.

Q-Pan is licensed for adults at increased risk of exposure. The following table defines persons at increased risk of occupational exposure to the H5N1 virus in the US:

Occupational exposure (includes not an exhaustive list)	Work involves	Risks contemplated	
Laboratory worker	• H5N1 vaccine manufacturer • Antiviral drug developer • Diagnostic test developer • Investigator • Laboratory technician • Student or post-doctoral candidate	Contact or works with live influenza A (H5N1) virus or clinical samples from suspect cases	Mechanical malfunction, human error, accidents, natural disasters, gaps in respiratory or other protections
Experimental animal study worker	• Veterinarian • Animal care technician	Contact with or care for influenza A (H5N1)-inoculated or infected animals, secretions or products	Unexpected animal behavior, bites, injuries, gap-in respiratory and other protections
Public health responder (human health)	• EIS officer • Epidemiologist • Infection control specialist • Environmental specialist	Investigating or managing suspected or confirmed human case(s) of influenza A (H5N1) infection	Gaps in respiratory protection due to malfunctions, accidents
Public health responder (animal health)	• Field veterinarian • Field animal health technicians (e.g., diagnostic sampling) • EIS officer • Epidemiologist	Investigating suspected or confirmed avian case(s) of influenza A (H5N1) infection or suspected cases in other species	Gaps in respiratory protection due to malfunctions, accidents or unexpected animal behavior.
Other	• Ancillary staff entering laboratory (e.g., service technician, janitor, informatics technician)	Potential for contact with live influenza A (H5N1) virus or inoculated/infected animal in a laboratory	Gaps in respiratory protection due to malfunctions, accidents or unexpected animal behavior

*H5N1 is used herein to denote any H5 subtypes with the A/goose/Guangdong/96 lineage H5

Given that persons at increased risk of exposure to H5N1 virus are a fairly narrowly defined group, it was important to estimate the size of the population and thus the possible vaccine demand. In 2014, there were 173 Principal Investigators (PIs) who had licenses to work with highly pathological avian influenza viruses. Each of the three PIs at CDC has about 15 laboratorians, so it was estimated that in the US, about 2500 laboratory workers may have an interest in being vaccinated. There are approximately 250 public health responders. Based on this estimation, the total number of laboratory workers and public health responders at increased risk is fairly low at approximately 3000 total persons. At 2 doses per person, that would be approximately 6000 doses of vaccine.

It was also important to quantify the risk of an exposure to H5N1 virus in these persons in order to appropriately weight the risks against the benefits. In the US, highly pathogenic avian influenza viruses are regulated by the US Department of Agriculture (USDA) as Select Agents under Code of Federal Regulation (Title 9, Part 121). The Select Agent regulations require entities in the US to do the following, "An individual or entity must immediately notify the Animal and Plant Health Inspection Service (APHIS) or CDC upon discovery of a release of a select agent or toxin causing occupational exposure or a release of a select agent or toxin outside of the primary barriers of the biocontainment area."

Between 2007 and 2013, there were 44 reported incidents or an average of 6 per year. The types of incidents reported include needlesticks, animal bites, leaks, work outside a containment facility, or failure in equipment of personal protective equipment (PPE). It is important to note that an incident does not necessarily equate to an exposure. For example, a needle stick injury with a solution and no virus could still be reported and included here. Based on a review of the reports, the annual frequency of incidents per laboratory worker was estimated to be <1% per year. None of these reported incidents resulted in infection. In other words, no persons were infected.

In summary, H5N1 remains a global concern and it has a high mortality rate. The US has two licensed vaccines, one of which is being made post-licensure. The total population at increased risk of occupational exposure is small. The available data suggest that the risk of transmission through occupational exposure is zero to extremely low. There are some limitations.

Laboratory events certainly could have gone unreported, which would have underestimated the number of incidents. In addition, reporting is not restricted to H5N1. It includes other HPAI viruses, which could have resulted in an overestimation. However, it is known that most of these reported incidents were related to H5N1. Finally, no systematic data are collected on public health responders, but it is known that there have been no infections in public health responders.

Discussion Points

Dr. Harrison was unclear about the issue of the adjuvanted vaccines and the issue of narcolepsy in terms of whether this is a vaccine-specific issue, antigen-specific issue, or adjuvant-specific issue.

Dr. Olsen replied that the issue is unclear.

Dr. Shimabukuro (ISO) added that the findings have been observed in Pandemrix[®], the monovalent H1N1 vaccine that was widely used in Europe and the study Dr. Olsen mentioned in Quebec. There is a CDC study underway to assess Adjuvant System 03[®] (AS03[®]) and MF59[®] adjuvanted vaccines for which preliminary results should be available in late 2015.

Dr. Reingold requested further information about whether this vaccine is in bulk, what the shelf-life is, and what the commitment to continuing to have stockpiles will be.

Dr. Olsen responded that currently, the vaccine is kept in bulk at the manufacturer's facility. The antigen and adjuvant are separate. In terms of the supply, there is already a precedent. Some of the vaccine was sent to NIH for clinical trials. NIH has prepared and distributed the vaccine, so there is a mechanism in place through NIH for some of the delivery. However, some delivery issues still need to be worked out.

Dr. Gellin (NVPO) added that the vaccine stock is managed in bulk so that formulation can occur at the right quantities when needed. That is the plan going forward and there is no endpoint to that at this time. Currently, there are a number of clades in the stockpile that can be handled in the same way. When the product is in bulk, it does not have a shelf-life.

Given the number of clades, Dr. Orenstein (NVAC) asked whether there are any data from animal studies regarding cross-protection or antibody events. That is, would this vaccine induce antibodies against the other clades as well as its own clade?

Dr. Olsen indicated that in general there is a diminished response, and that the data on heterologous immunity can be found in the extra slides that she did not present during this session. The response depends upon the virus being tested against the vaccine.

Dr. Belongia inquired as to the level of exposure of the estimated 2600 people who should receive this vaccine.

Dr. Olsen responded that this is a rough calculation based on information known about PIs at CDC. There is variability in terms of how much someone works in the laboratory.

GRADE and Policy Options for Influenza A (H5N1) Vaccine

Sonja J. Olsen, PhD

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Olsen reminded everyone that the WG was charged to answer the policy question, “Should licensed influenza A (H5N1) vaccine be recommended to adults with increased risk of exposure during the inter-pandemic time period?” First, the WG members enumerated all possible outcomes of interest, independent of whether data were available. Each member independently scored outcomes using the following numerical scale:

- Critical to decision making (7-9)
- Important, not critical (4-6)
- Low importance (1-3)

The rankings were then summarized. Safety and immunogenicity outcomes were identified, which are shown in the following tables:

Outcome	Importance
Any vaccine-related serious adverse event	Critical
Anaphylaxis or immediate hypersensitivity	Critical
Narcolepsy	Critical
Guillain-Barré syndrome	Critical
Other serious neurologic outcomes (e.g., encephalitis, transverse myelitis, Bell's palsy, acute disseminated encephalomyelitis, other acute demyelinating diseases)	Critical
Mortality	Critical
General symptoms (fatigue, headache, joint pain, muscle aches, chills, malaise, nausea, shivering, sweating)	Important
Syncope	Important
Fever	Important
Injection site reactions (pain, tenderness, redness, swelling)	Low

Outcome	Definition	Importance	
21-day	homologous seroprotection	% of subjects achieving $\geq 1:40$ HI ab titer to A/Indonesia/05/2005	Critical
	homologous seroconversion	% of subjects achieving seroconversion to A/Indonesia/05/2005	Critical
	heterologous seroprotection	% of subjects achieving $\geq 1:40$ HI ab titer to currently circulating strains and strains in vaccine development	Important
	heterologous seroconversion	% of subjects achieving seroconversion to currently circulating strains and strains in vaccine development	Important
6-month	homologous seroprotection	% of subjects achieving $\geq 1:40$ HI ab titer to A/Indonesia/05/2005	Important
	homologous seroconversion	% of subjects achieving seroconversion to A/Indonesia/05/2005	Important
	heterologous seroprotection	% of subjects achieving $\geq 1:40$ HI ab titer to currently circulating strains and strains in vaccine development	Important
	heterologous seroconversion	% of subjects achieving seroconversion to currently circulating strains and strains in vaccine development	Important

*Seroconversion = % of subjects with a pre-vaccination HI titer < 10 and a post-vaccination titer ≥ 40 or with a pre-vaccination HI titer (Day 0) ≥ 10 and a fold-increase (post/pre) ≥ 4 .

The next step was to define the data to review. To do this, it is helpful to understand what vaccines there are. GSK's H5N1 AS03 adjuvanted vaccines are manufactured in two different places. This is relevant because the manufacturing process differs between the two plants. Pumarix/Q-Pan is manufactured in Québec, Canada and contains A/Indonesia/05/2005 Clade 2.1. Prepandrix/D-Pan is manufactured in Dresden, Germany and contains A/Vietnam/1194/2004 Clade 1 and A/Indonesia/05/2005 Clade 2.1. The vaccine of interest is the FDA-licensed vaccine Pumarix/Q-Pan containing A/Indonesia/05/2005.

In addition, GSK makes a number of seasonal influenza vaccines and has made pandemic influenza vaccines as shown in the following table:

Vaccine	Description	Manufacturer Location	Haemagglutinin (HA) per 0.5 mL dose	Adjuvant
Seasonal Vaccines				
FluLaval®	U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion)	Québec, Canada	15 µg HA	None
FluLaval® Quadrivalent	U.S.-licensed seasonal influenza vaccine (inactivated, split virion)	Québec, Canada	15 µg HA	None
Fluarix®	U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion)	Dresden, Germany	15 µg HA	None
2009 Pandemic Vaccines				
Arepanrix™	GSK's H1N1 AS03- adjuvanted pandemic vaccine	Québec, Canada	3.75 µg HA	AS03 _A
Pandemrix™	GSK's H1N1 AS03- adjuvanted pandemic vaccine	Dresden, Germany	3.75 µg HA	AS03 _A

The WG decided that it would be difficult to extrapolate data for some of these other vaccines due to differences in the manufacturing process in Québec versus Dresden; antigen content (3.75µg vs. 15µg); and adjuvant (none vs. AS03). In addition, avian H5 HA is less immunogenic than those of human influenza viruses. For those reasons, the WG chose to focus on data using the Q-Pan vaccine manufactured in Quebec.

As part of the literature review, the key terms searched were H5N1 vaccine AND Indonesia; a few additional references were provided by the manufacturer. Several of the WG members independently reviewed the abstracts from all of the 108 studies found with the key term search and the 5 provided by the manufacturer. Full article reviews were conducted on 20 papers. Of those, 16 were excluded because the primary vaccine strain differed or was made in the wrong plant and the following 4 studies were included and were assessed in detail:

Studies Considered					
Paper	Design	Arms	Ages (yr)	Setting	Outcomes
Langley (2010)*	Phase 1/2 Randomized (no placebo) Observer blinded	1. Nonadjuvanted 2. AS03 _A Quebec 3. AS03 _A Dresden 4. AS03 _B Quebec 5. AS03 _B Dresden	18-64	United States, Canada	Safety, Immunogenicity
Langley (2011)*	Phase III Randomized Placebo-controlled Observer-blinded	1. Vaccine, 18-64yr 2. Placebo, 18-64yr 3. Vaccine, ≥65yr 4. Placebo, ≥65yr	≥18	North America	Safety, Immunogenicity
Laskos (2011)	Phase II Randomized (no placebo) Open-label	1. Vaccine days 0/21 2. Vaccine days 0/14 3. Vaccine days 0/7 4. Vaccine days 0/0	18-64	Canada	Safety, Immunogenicity
Nagai (2011)	Phase II Open-label No comparison group	1. Vaccine, 20-40yrs 2. Vaccine, 41-64yrs	20-64	Japan	Safety, Immunogenicity

Red = Q-pan

*Data from these studies used in FDA's Summary Basis of Regulatory Action.

The WG reviewed data from all four manuscripts. Langley (2010) was an RCT with no placebo. Its question focused on different adjuvant doses (full vs. half) and different manufacturing sites (Quebec vs. Dresden). Langley (2011) was an RCT with a placebo. Laskos (2011) was an RCT with no placebo that compared different dosing schedule. Nagai (2011) was a descriptive study with no comparison group. All studies assessed safety and immunogenicity. The one study that was designed to answer the WG's question (vaccine yes/no) was the Langley (2011) placebo-controlled study, which is the study the WG used to GRADE the evidence. For those interested, Dr. Olsen noted that the data from all four studies were included as extra slides. The outcomes available from the Langley (2011) study are shown in the following table:

Outcomes Available				
Outcome			Importance	Langley 2011
Harms				
Any vaccine-related SAE			Critical	✓
Anaphylaxis, immediate hypersensitivity			Critical	-
Narcolepsy			Critical	-
Guillain-Barré syndrome			Critical	-
Other serious neurologic outcomes			Critical	-
Mortality			Critical	✓
General symptoms (listed individually)			Important	✓
Syncope			Important	✓
Fever			Important	✓
Benefits				
21-day	homologous	seroprotection	Critical	✓
		seroconversion	Critical	✓
	heterologous	seroprotection	Important	-
		seroconversion	Important	-
6-month	homologous	seroprotection	Important	✓
		seroconversion	Important	✓
	heterologous	seroprotection	Important	-
		seroconversion	Important	-

As reflected in the table, several of the critical safety outcomes were missing and data were available only on the homologous etiologic outcomes.

For the safety outcome of any vaccine-related SAE (ranked as critical), imprecision was downgraded because the sample size was too small to detect rare SAE. This resulted in the quality of evidence being rated as Moderate (2). The quality of evidence for mortality (also ranked as critical) was rated as High (1). The quality of evidence for the safety outcomes ranked as important (fatigue, headache, joint pain, muscle aches, and shivering) was rated as High (1). For the outcome of sweating (ranked as important), imprecision was downgraded because the confidence interval included 1; therefore, the quality of evidence was rated as Moderate (2). For the outcome of syncope (ranked as important), imprecision was downgraded due to the small sample size and thus the inability to detect a rare event; the quality of evidence was rated as Low (3). Imprecision was downgraded for the outcome of fever (ranked as important) due to the wide confidence interval, and the quality of evidence was rated as Moderate (2).

In terms of immunogenicity outcomes ranked as critical, the quality of the evidence was considered to be High (1) for 21-day homologous seroprotection and 21-day homologous seroconversion. For the immunogenicity outcomes ranked as important, 6-month homologous seroprotection and 6-month homologous seroconversion, imprecision was downgraded for small sample sizes and wide confidence intervals and the quality of the evidence was considered to be Moderate (2). Overall, the WG rated the quality of evidence as Moderate (2).

There are other considerations in addition to the GRADE data for formulation of recommendations. The first is to consider the balance between the benefits and harms. The issues the WG weighed were that the evidence was based on a single study; the benefits may not be generalizable due to Clade evolution; data were absent for 4 of the 6 critical harms, resulting in uncertainty about balance of benefits vs. harms; there were no data on efficacy; the risk of exposure is low; and there is a zero to low transmission risk. Overall, the evidence type was Moderate (2) for safety and High (1) for immunogenicity. In terms of values and preferences, there were no data regarding how the target group values the outcome. The potential recipients were few in number (<3,000) in the US. Usually, these analyses take into account health economic data, which is not really relevant here because the vaccine is paid for by US government so it was not considered.

For consideration and discussion during this session, the WG put forward the following draft recommendation for influenza A (H5N1) vaccine:

DRAFT Recommendation for Influenza A (H5N1) Vaccine

- Category B
 - Adults aged ≥18 years with increased risk of occupational exposure during the inter-pandemic period may receive adjuvanted influenza A (H5N1) vaccine for protection against infection with influenza A (H5N1)*
- Intervention: Q-Pan, 2 doses administered 21 days apart
- Occupational exposure defined as follows
 - Laboratory workers who have contact or works with live influenza A (H5N1) virus or clinical samples from suspected cases
 - Experimental animal study workers who have contact with or care for influenza A (H5N1)-inoculated or infected animals, secretions or products
 - Public health responders investigating or managing suspected or confirmed human case(s) of influenza A (H5N1) infection
 - Public health responders investigating suspected or confirmed avian case(s) of influenza A (H5N1) infection
 - Others who work in locations where exposure to influenza A (H5N1) virus could occur

*H5N1 is used herein to denote any H5 subtypes with the A/goose/Guangdong/96 lineage H5₂₆

Discussion Points

Dr. Kempe asked for clarification about when the additional safety data will be available and whether it will contain all of the critical elements that are currently lacking. She did not understand what additional data CDC is collecting regarding safety.

Dr. Olsen replied that additional data are not anticipated specific to this vaccine. Data are expected in 2015 from the CDC-sponsored narcolepsy study, which is not specific to this vaccine. The CDC study is assessing monovalent vaccines from the 2009 pandemic that contained the same adjuvant. Also, it is important to remember that it is necessary to vaccinate a large number of people in order to find very rare outcomes, which will not be done with H5N1 vaccine.

Dr. Shimabukuro (ISO) added that the CDC-sponsored study on narcolepsy is assessing 2009 monovalent H1N1 adjuvanted vaccines that contained AS03[®] or MF59[®] used in countries outside of Europe. That does not pertain to the vaccine Dr. Olsen was discussing.

Dr. Rubin asked whether the placebo recipients in the primary trial received the adjuvant as part of the placebo, and whether this is a purified hemagglutinin (HA) or a split vaccine with the amount of HA indicated.

Dr. Leonard Friedland (GSK) replied that the vaccine used in the placebo arm did not contain adjuvant. This is a split, inactivated subvirion vaccine similar to the seasonal vaccines used. In this case, it was for H5N1.

Dr. Reingold asked whether he understood correctly that ACIP would be asked to vote on a recommendation for use of the H5N1 vaccine during the February 2015 meeting. He noted that the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) went through a similar process for pandemic influenza vaccine. He was on that working group and found that to be a difficult discussion. One item discussed was “storage” of the vaccine in humans; that is, priming large numbers of individuals with a first dose so that if there is a pandemic, only one additional dose would have to be given to those individuals to achieve protection versus having to dispose of large quantities of vaccine when it reaches the end of its self-life. There was also discussion of other potential populations who should be protected in the event of a pandemic. It sounded like in terms of policy, the Novel Influenza WG had already focused on this group.

Dr. Olsen replied that this was only tangentially discussed because the group was focused on a specific question and did not want to become sidetracked. Ultimately, the SAGE recommendation said that there were not enough data to recommend priming.

Dr. Belongia noted that there is a spectrum of potential exposures among people who fall within these categories, such as people who have rare occasional exposures to samples or people who have repeated frequent exposures. Given the uncertainties and the limited amount of data currently available regarding safety, it would be helpful to clarify that this pertains to people who have repeated or frequent potential exposures rather than people who have rare or uncommon exposures.

Dr. Olsen replied that the WG discussed this. There are no data addressing frequency of exposure and there are no transmission events. The WHO recommendations discuss work with large amounts of virus or work with virus for extended periods of time; however, they do not quantify any of that. The WG decided that this was too nebulous and it would be clearer to say someone who does or does not work with the virus. The WG can further consider this issue.

Dr. Sun (FDA) indicated that as with all vaccines, subsequent to the FDA approval of Q-Pan H5N1, the manufacturer is required to evaluate the vaccine in children and conduct additional safety studies.

Dr. Leonard Friedland (GSK) indicated that a pediatric study was conducted in infants 6 months through 17 years of age. GSK recently shared the findings with the FDA, and discussions are underway to amend the Biologics License Applications (BLA) in the future to include a license indication below the current age of 18.

Dr. Weber (SHEA) requested further clarification of the meaning of “public health responders.” For example, he has a colleague on his campus who works with emerging viral diseases. If that individual is exposed, he would be required by policy to present to the hospital’s emergency department (ED) to be evaluated and possibly be admitted. Would “public health responders” include the 300 members of the ED Care Team who would take care of him, as well as the Occupational Health Department?

Dr. Olsen clarified that “public health responders” would include US healthcare personnel (HCP) deploying someplace to investigate illness. For example, this would include HCP going to Indonesia to investigate a cluster of illness due to H5N1 in humans or an H5N1-associated poultry die-off. Because there are no cases in the US, this does not include HCP or first responders in the US. The WG understands that the situation is fluid and could change in the future.

Dr. Orenstein (NVAC) was intrigued by the statistically significant 5-fold reduction in mortality in the vaccinated group. He presumed that they thought this was a statistical artifact, but wondered whether there was any biologic plausibility to that. Many people are involved in research studies conducting surveillance for influenza in various animal populations domestically and abroad. He presumed that unless this work was being done specifically in a high-risk H5N1 situation, those people would not fit into the risk category for receiving the vaccine.

Dr. Olsen replied that in terms of the 5-fold reduction in mortality, these were not vaccine-associated deaths. This was mortality that occurred during the study, primarily in older persons. This did not raise concerns among the WG members. The investigators conducting influenza surveillance would not be included in the risk category for receiving the vaccine.

Dr. Bennett pointed out that not long ago, many people in this country were vaccinated against smallpox. The wording was very similar, and there may be a lot of opportunity for misinterpretation. It might be useful to describe more specifically what is meant by “public health responders.”

Thinking about the public health responders who may go to several outbreaks and laboratorians who have frequent and repeated exposures to these viruses, Dr. Schaffner (NFID) was interested in the anticipated duration of immunity. He wondered whether consideration was being given to one-time immunization versus re-immunization of those who have frequent and repeated exposures over time.

Dr. Olsen replied that while this is a good question, it was not addressed by the WG. The 6-month immunogenicity outcomes were assessed, and the immune response was found to be diminished. There are no data to assess that the need to a booster dose because they do not have longer outcomes.

Dr. Loehr (AAFP) disagreed with the statement that the health economic analyses is not relevant because it is paid for by the US government. If the cost of a vaccine was \$1 million per dose versus \$10 per dose, that would be relevant. If there is no evidence of laboratory transmission, he wondered whether laboratory workers need this vaccine. Also, are animal study workers more at risk than laboratory workers because they are handling infected animals? Those issues have not been teased out.

Dr. Olsen said she appreciated what Dr. Loehr said about cost, and that the WG could revisit the health economic analysis issue. There are no known cases of transmission in a public health responder or laboratory worker. That contributed to the recommendation of a Category B rather than Category A. The WG can also discuss this further.

Dr. Temte asked if there have been any reports of routine administration of antivirals in the case of laboratory breaches.

Dr. Olsen responded that in general, this would be the recommendation, but she did not know how many had taken antivirals.

Dr. Harrison did not think much guidance was actually provided, and wondered whether there had been any discussion in the WG about creating a clear recommendation.

Dr. Temte responded that there is the option for a Category A recommendation, which uses language such as “should receive.” The WG engaged in significant deliberation about this issue, and felt that Category B was appropriate for individual clinical decision-making based on one’s own exposure and concern about that exposure, plus all of the unknowns in terms of the risks and long-term benefits. Despite ACIP’s disdain for Category B recommendations, the WG felt that a Category B recommendation was appropriate in this situation.

Dr. Kempe pointed out that the key will be the risk/benefit information given to people. This in itself simply allows people to obtain the vaccine.

Dr. Temte expressed appreciation for the depth of the discussion, which can go back to the WG for further consideration and modification prior to the February 2015 ACIP meeting.



Introduction

Art Reingold, MD Chair, ACIP Pertussis Vaccine Work Group

Dr. Reingold reminded everyone that the terms of reference for the Pertussis Vaccine WG are to:

- Review existing statements on infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate them into a single statement.
- Review new data on Tdap including
 - Effectiveness of ACIP recommendations
 - Interval between Td booster and Tdap
 - Use of Tdap in adults ages 65 years and older
 - Pregnant and breastfeeding women
 - Use of Tdap
 - Cocooning strategies
 - Vaccinated HCP and need for post-exposure prophylaxis
 - Tdap revaccination
 - Pregnant women
 - Healthcare personnel
 - “Cocooning”
- Review updated epidemiology of tetanus and diphtheria in the US

Two Tdap products are licensed in the US, both of which are licensed for single use. GSK's BOOSTRIX[®] vaccine has an age indication of 10 years and older, while Sanofi Pasteur's ADACEL[™] vaccine has an age indication of 10 through 64 years of age. The current ACIP recommendations for Tdap and Td is for a single Tdap dose for all persons aged 11 years and older, preferred administration at 11 or 12 years of age. Pregnant women are recommended to receive Tdap with every pregnancy. This is primarily designed to provide protection to the newborn baby. A decennial Td booster is recommended for those who have received 1 Tdap vaccine, and a booster is recommended at 5 years for wound management. Diphtheria, tetanus, and acellular pertussis (DTaP) vaccine coverage among children is high and adolescent Tdap coverage has greatly improved; however, adult Tdap coverage remained low at 14% as of 2012. Tdap coverage is also low among pregnant women at approximately 15%.

Administering Tdap to pregnant women raises safety concerns. There have been 62 Tdap reports in pregnant women to the Vaccine Adverse Event Reporting System (VAERS) since the last ACIP update in February 2014. Tdap was given during the third trimester in 66% of reports with data on gestational age at time of vaccination. Of the reports, 53 were non-serious reports. There were 9 serious reports, including 1 neonatal death that was due to umbilical cord occlusion with fetal vascular thrombus formation. Conditions among other serious reports included 2 non-anaphylaxis allergic reactions and 1 report each of elevated blood pressure/abdominal pain, severe headache, rhabdomyolysis, multiple systemic symptoms (e.g. fever, chills, myalgias), pneumonia, and hypoglycemia in an infant. Overall, there were no concerning patterns of adverse events.

CDC's Immunization Safety Office (ISO) monitors maternal Tdap safety through VAERS, in which no safety signals have been identified. Safety data from the VSD on obstetric events and birth outcomes were presented during the February 2014 ACIP meeting. Analyses of VSD data are in progress regarding the interval between prior tetanus-toxoid containing vaccines and current Tdap vaccination, and concurrent administration of Tdap and influenza vaccines. The Clinical Immunization Safety Assessment (CISA) Project has implemented a prospective observational clinical study of Tdap safety in pregnant women [Vanderbilt University and Duke University; registered at ClinicalTrials.gov NCT02209623]. The WG has also requested additional data from the military or other groups that may have extensive experience with use of the vaccine in pregnant women, and is trying to maintain as much awareness as possible regarding what is occurring in pregnancy.

June 2013, ACIP took into consideration that there is an increasing burden of pertussis, with a substantial burden nationally; that there is good evidence to suggest that a second dose of Tdap is safe and immunogenic; that protection wanes in a few years after Tdap; and that the cost-effectiveness model suggests that a reduction of the disease burden would be limited with a second dose of Tdap.

In June 2014, ACIP concluded that the public health impact of routinely recommending a second dose of Tdap would be limited, and that no change should be made to the current Tdap recommendation. ACIP recognized that the focus should be on preventing pertussis in infants, and ensuring that pregnant women receive Tdap during each pregnancy. ACIP supported the WG to consider additional doses for special populations, including HCP and close contacts of infants.

This session included presentations on Tdap vaccine, pertussis in HCP, the impact of vaccinating HCP, and the WG's conclusions.

HCP Pertussis and Tdap Vaccination

Jennifer L. Liang, DVM, MPVM
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

As Dr. Reingold noted, ACIP made considerations over a year ago for a second dose of Tdap for the general population but did not change the current recommendation. Since then, the WG has considered Tdap vaccination of HCP and evaluated the need for and potential impact of additional doses of Tdap. For today's discussion, Dr. Liang presented a summary of these data and the WG's conclusions.

Currently, both Tdap vaccines are licensed only for a single dose. As previously reviewed by ACIP, a second dose of Tdap is safe and immunogenic. There are several published clinical trials from other countries on a second dose of Tdap at 5 or 10 years after the first dose. Reported adverse events were generally comparable to those after the first Tdap. The majority of local and systemic adverse events were mild to moderate and self-limited. Of the few serious adverse events reported, none were determined to be related to receipt of the second Tdap. Safety profiles were comparable at the 5 and 10 year intervals. For immunogenicity after receipt of a second Tdap, tetanus and diphtheria are essentially 100% protected. For the pertussis components, responses are similar at 5 and 10 year intervals. Response is also comparable to historic and contemporaneous first dose.

After a single dose of BOOSTRIX[®], similar geometric mean concentration (GMC) curves are observed through 10 years. Response to a second BOOSTRIX[®] after a 10-year interval was similar to the response after the first at a 10-year interval. A second dose of ADACEL[™] at a 10-year interval also showed similar response after a first dose. For ADACEL[™], after a 5-year interval, response to a second Tdap was robust, but was lower compared to the response after the first dose. But at 5 years, the baseline for pertussis antibodies before a second Tdap were higher.

In the US, both pharmaceutical companies are conducting clinical trials of a second dose of Tdap. Sanofi Pasteur's US study for ADACEL[™] is complete and was presented to the WG and summarized to ACIP in February 2013. A revaccination study in Canada will finish later this year and Sanofi Pasteur plans to submit to FDA consideration of label updates for ADACEL[™]. GSK's revaccination program for BOOSTRIX[®] is also underway. One revaccination study of young adults who received their first Tdap as adolescents 10 years earlier is complete. A revaccination study in adults is underway. GSK plans to submit data to FDA for consideration of label updates to BOOSTRIX[®] that will be dependent on pertussis epidemiology and ACIP recommendations.

Tdap is effective, but protection starts to wane within three years. Previous estimates of Tdap vaccine effectiveness range between 66% to 78%. However, all of these studies involved adolescents who received some whole cell vaccines as part of their childhood series. At the time, the effectiveness of Tdap among adolescents who had received all acellular vaccines in childhood was unknown. During the 2012 epidemic in Washington, the CDC in collaboration with the Washington State Department of Health conducted a large-scale vaccine effectiveness

study in adolescents who only received acellular pertussis vaccines. Estimated Tdap VE was 65%, which is consistent with previous studies. This study also assessed the duration of protection [Rank C, et al. *Pediatr Infect Dis J*. 2009 28(2):152-3; Wei SC, et al. *CID* 2010 51(3):315-321; Skoff et al. *NIC* 2011, Washington, DC; Acosta A, et al. Publication pending].

During the 2012 pertussis epidemic, Wisconsin² also evaluated Tdap vaccine effectiveness and duration of protection in their adolescent population that also only received acellular vaccines. Despite the methodologies being different, both studies demonstrated substantial waning of protection over time. In Washington¹, the initial effectiveness within 12 months of Tdap vaccination was 73%. Following this, the effectiveness declined substantially. Between 2 and 4 years post-vaccination, the VE was only 34%. This waning in protection is consistent with the observed epidemiology. Wisconsin published results that were very similar to CDC's findings showing that Tdap vaccine effectiveness decreased with increasing time since receipt [¹Acosta et al. *Tdap Vaccine Effectiveness and Duration of Protection Among Adolescents During the 2012 Washington State Pertussis Epidemic*. Publication pending; ²Koepke et al. *Estimating the Effectiveness of Tdap Vaccine for Preventing Pertussis: Evidence of Rapidly Waning Immunity and Differences in Effectiveness by Tdap Brand*. *The Journal of Infectious Diseases* 2014].

For indirect protection, it is unclear what the effect of Tdap vaccination is on preventing pertussis transmission. For people vaccinated with acellular pertussis vaccines, symptoms are not as severe and presumably less likely to transmit. An Australian cocooning case-control study found a modest decrease in the risk of pertussis in infants whose mothers were vaccinated at a sufficient time to boost their immune response relative to the infants' pertussis incubation period. This effect was also seen in infants whose mothers were vaccinated post-partum. But it is unclear whether the lower risk for infants was attributable to a short-term impact on transmission for recently vaccinated mothers or lack of exposure to infants [Quinn HE et al. *Parental Tdap boosters and infant pertussis: a case-control study*. *Pediatrics*. 2014 Oct;134(4):713-20].

An animal model showed that acellular pertussis vaccinated baboons were protected against disease but not infection. Bacterial colony counts from nasopharyngeal washes were comparable to those observed in unvaccinated animals. Infected but asymptomatic baboons transmitted pertussis to other cohoused baboons. Although these results are striking, it is unclear if this animal model represents what happens with humans, vaccines, and infection. There is currently no human challenge model [Warfel JM et al. *Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model*. 2014 Jan 14;111(2):787-92].

Pertussis occurs in HCP, but probably is not a significant contribution to the overall burden of disease. Occupational exposures to pertussis occur in health-care settings. The frequency and proximity of patient interaction puts HCP at increased risk for infection with the potential to expose many.

Nosocomial infections in health-care settings have been documented. The index case has been identified as an HCP, patient, or hospital visitor. There have been numerous published reports of pertussis outbreaks in a variety of health-care settings. Anecdotally, states recently hard-hit with pertussis have not identified or reported health-care outbreaks, including California, Wisconsin, and Washington. The last one reported to CDC was in 2011 [Valenti WM, et al. 1980; Steketee RW, et al. 1988; Fisher MC, et al. 1988; Addiss DG, et al. 1991; Christie CDC, et al. 1995; Shefer A, et al. 1995; CDC. *MMWR* 2005;55(03); Boulay BR, et al. 2006; Pascual

FB, et. al. 2006; Vranken P, et. al. 2006; Bryant KA, et. al. 2006; Zivna I, et. al. 2007; Baggett HC, et. al. 2007; CDC. *MMWR* 2008;57(22); Leekha S, et. al. 2009; Yasmin S, et. al. 2013].

The measured risk and burden of disease in HCP are not well-defined. National surveillance does not collect HCP status for pertussis cases. There are few population-based estimates on the relative risk of pertussis for HCP. One study in the Province of Quebec estimated a 1.7 fold increased risk for HCP compared to their adult population. This was based on 384 reported adult pertussis cases, 32 of which were HCP. Another study found 1.3% to 3.6% annual incidence in emergency department residents, nursing, and patient-care staff. Incidence was based on serologic evidence. Some infections were asymptomatic. Published studies note that yearly infection rates among adolescent and adults varied from 1% to 6%, based on serologic studies. In general, the risk among HCP and the general population is comparable [Deserres G, et al. Morbidity of pertussis in adolescents and adults. *J Infect Dis* 2000; 182:174-179; Wright, SW, Decker MD, Edwards KM. Incidence of pertussis infection in healthcare workers. *Infect. Control Hosp. Epidemiol.* 1999. 20:120-123; Cherry JD. The present and future control of pertussis. *Clin Infect Dis.* 2010 Sep 15;51(6):663-7].

Pertussis exposure management in health-care settings is complicated, time-consuming, and costly. Several studies have estimated the cost of investigation and control measures which are substantial; however, Tdap vaccination would not change that [Zivna I, et al. Impact of *Bordetella pertussis* exposures on a Massachusetts tertiary care medical system. *Infect Control Hosp Epidemiol.* 2007 Jun;28(6):708-12; Calugar A, et al. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. *Clin Infect Dis.* 2006 Apr 1;42(7):981-8; Baggett HC, et al. Two nosocomial pertussis outbreaks and their associated costs - King County, Washington, 2004. *Infect Control Hosp Epidemiol.* 2007 May;28(5):537-43; Yasmin S et al. Healthcare-Associated Pertussis Outbreak in Arizona: Challenges and Economic Impact, 2011. *J Ped Infect Dis.* 2013 3(1):81-84].

Current guidance on post-exposure prophylaxis (PEP) for HCP is based on likely contact with patients at risk for severe disease and not Tdap vaccination status. One study looked into the need of PEP for Tdap vaccinated HCP, but the results were inconclusive. Very few exposed HCP were infected regardless of PEP or not. Infection was based on serologic evidence and none was symptomatic. These HCP were vaccinated within 4 years prior to their exposure [CDC. Immunization of Health-Care Personnel Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011 60(No. SS-7): 1-45; Goins WP et al. A Comparison of 2 Strategies to Prevent Infection Following Pertussis Exposure in Vaccinated Healthcare Personnel. *Clin Infect Dis.* 2012 Apr;54(7):938-45].

Since 2006, HCP have been recommended to receive a single dose of Tdap and a routine Td booster every 10 years. Hospital-based Tdap coverage rates vary, and a lot of effort has been put into increasing coverage from campaigns to mandates. As we approach 10 years since the introduction of Tdap, national HCP coverage for the first dose is 31% [Calderon M, et al. Implementation of a pertussis immunization program in a teaching hospital: an argument for federally mandated pertussis vaccination of health care workers. *Am J Infect Control.* 2008 Aug;36(6):392-8; Weber DJ, et al. Assessment of a mandatory tetanus, diphtheria, and pertussis vaccination requirement on vaccine uptake over time. *Infect Control Hosp Epidemiol.* 2012 Jan;33(1):81-3; CDC. Noninfluenza Vaccination Coverage Among Adults — United States, 2012. *MMWR.* 63(05);95-102].

The benefits and costs of vaccinating HCP with Tdap were modeled previously to look at preventing a nosocomial pertussis outbreak. Vaccinating HCP was shown to substantially reduce the risk of hospital-based outbreaks and was cost-effective/cost-saving. But model inputs included Tdap vaccine efficacy estimates higher than current estimates and assumed vaccination would decrease transmission and prevent secondary cases. At this time, there is no direct evidence and the role of vaccination in transmission and prevention is unclear. There are plans to update the CDC's model [Greer AL, Fisman DN. Keeping vulnerable children safe from pertussis: preventing nosocomial pertussis transmission in the neonatal intensive care unit. *Infect Control Hosp Epidemiol.* 2009 Nov;30(11):1084-9; Greer AL, Fisman DN. Use of models to identify cost-effective interventions: pertussis vaccination for pediatric health care workers. *Pediatrics.* 2011 Sep;128(3):e591-9; Calugar A, et al. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. *Clin Infect Dis.* 2006 Apr 1;42(7):981-8].

The WG has struggled with the lack of updated disease and vaccine data specific to HCP and are left with a number of uncertainties. Over the past several years, more has been learned about acellular pertussis vaccines. In acellular-primed adolescents, Tdap is effective but protection wanes substantially within a few years. For adults who were vaccinated with whole-cell pertussis vaccines, Tdap provides protection but would be difficult to study or better characterize. As the population ages, there will soon be more adults who received only acellular pertussis vaccines. Is the assumption valid that Tdap vaccination protects contacts? The evidence is unclear. Also, with the timing of any potential indication on additional doses of Tdap, does the committee wait or are we compelled to make an off-label recommendation?

After much discussion, the WG has made a number of observations regarding pertussis and vaccinating HCP. The WG recognizes that pertussis transmission occurs in health-care settings and that the frequency and proximity of patient interaction puts HCP at increased risk of exposure to pertussis. However, it is unclear how much pertussis exposure results in disease. There is a lack of updated data specific to HCP. The WG also recognizes that it is no small thing to implement recommendations for HCP. There is no supportive evidence that additional doses would be beneficial in prevention of disease and transmission in a health-care setting. Even if additional Tdap doses are recommended, there would be no change to risk management of pertussis exposures.

At this time, the ACIP Pertussis Vaccines WG does not propose changes to the current Tdap recommendation for HCP. With a record of more than 48,000 pertussis cases reported in 2012, and 2014 numbers already higher than at this time last year, the WG acknowledges the current resurgence of pertussis, and the burden this places on state and local health departments and providers. The WG has expressed a desire for CDC to consider agency guidance on the role of repeat Tdap doses for HCP in response to outbreaks in health-care settings. CDC is considering potential guidance language for the CDC pertussis website that would include encouraging consultation with state public health and CDC during outbreaks in health-care settings since each outbreak is unique, and guidance should be catered to the situation. The focus should be on the current Tdap program. This includes improving adult coverage, including among HCP, and vaccinating pregnant women during every pregnancy to protect infants.

Dr. Liang mentioned some pertussis-related projects underway with CDC's collaborators that will help address some data gaps. Results from these studies will be presented at future ACIP meetings. There are several vaccine effectiveness studies underway, including DTaP and Tdap vaccine effectiveness with the emergence of pertactin-negative strains. Through EIP's enhanced pertussis surveillance, the clinical characteristics of vaccinated and unvaccinated pertussis cases will be evaluated. Also through EIP's enhanced pertussis surveillance, reported pertussis cases who work in a health-care setting are being identified. There are plans to update the cost-effectiveness model of vaccinating HCP. For the Tdap pregnancy recommendation, there is a cocooning and pregnancy Tdap evaluation and an infant blood-spot study to measure the effectiveness of maternal Tdap against pertussis.

In conclusion, Dr. Liang highlighted additional CDC activities related to the Tdap pregnancy recommendation, including the following:

- ❑ Assessment Branch (ISD/NCIRD)
 - Measuring Tdap coverage among pregnant women
 - PRAMS (with DRH/NCCDPHP)
 - Internet panel survey on pregnant women during influenza season
- ❑ Immunization Safety Office (DHQP/NCEZID)
 - Safety monitoring in pregnant women following Tdap administration
 - Vaccine Adverse Event Reporting System (VAERS)
 - Vaccine Safety Datalink (VSD)
 - Clinical Immunization Safety Assessment (CISA) Project
- ❑ Health Communications Science Office (NCIRD)
 - Formative Research Plans to Develop a Maternal Tdap Vaccination Campaign

Discussion Points

In terms of epidemiology, Dr. Temte wondered how transmittable pertussis is for someone who is asymptomatic.

Dr. Liang responded that people who have been exposed to pertussis who are colonized and asymptomatic are highly less likely to transmit because they are not coughing, so they are not actually spreading bacteria.

Dr. Bennett inquired about the potential for developing mandatory Tdap vaccination of HCP. The uptake of 31% is striking and is about what it was 5 to 10 years ago for influenza prior to mandatory programs.

Dr. Weber (SHEA) indicated that his hospital is 100% compliant, with the exception of a few people who have medical contraindications, because Tdap is required along with measles, mumps, and rubella (MMR) and varicella vaccines. Pertussis remains one of the most common exposures to HCP. Over the last 5 years, about 1 out of 200 of their HCP has been exposed to pertussis. They are offered PEP with azithromycin, and virtually all of them accept it. None of their HCP have developed pertussis in the last 5 years. At this time, there is insufficient evidence for the WG to make an evidence-based recommendation for revaccination. SHEA has pointed out the significant logistical problems; however, if ACIP recommends no revaccination, budgeting will be lost because many have budgeted into the future for this vaccine. At 10 years,

HCP will be getting their 10-year Td vaccines. If a few years later the evidence supports a booster, they will not be happy about needing an extra vaccine. He also noted the contradictory nature of requiring the vaccine for incoming first-year HCP who are at low risk when protection is known to wane, only to tell them later that they do not need a booster. That is difficult to sell, particularly as a requirement for initial work. The SHEA board members felt that if additional data are going to be available in the next few years, that initially it would be better to recommend a booster and then stop if necessary rather than trying to reinstitute one in the future.

Dr. Fryhofer (AMA) indicated that the AMA would be meeting in the upcoming week with the House of Delegates. A resolution was introduced by the Oregon State Delegation that expresses confusion about Medicare coverage of Tdap vaccinations. For the record, she requested clarification and specific input about how to administer Tdap vaccine within the office and get it covered.

Dr. Liang responded that currently, Tdap vaccination is covered in Part D of Medicare for those 65 years of age and older. It is not included as part of the routine Part B series.

Ms. Hance (CMS) added that she would follow up to see if she could acquire further information from her Medicare colleagues.

Dr. Temte said the follow-up question pertains to all of the ACIP-recommended immunizations for patients on Medicare in terms of what type of rule changes would be possible to ensure that all ACIP-recommended vaccines are covered under Part B.

Given 15% uptake of Tdap vaccine among pregnant women, Dr. Pickering requested that Dr. Ault from American College of Obstetricians and Gynecologists (ACOG) and Dr. Loehr from American Academy of Family Physicians (AAFP) comment on what those two organizations are doing to increase coverage among pregnant women.

Dr. Ault (ACOG) indicated that he and Dr. Riley are on ACOG's Immunization WG. One of ACOG's more successful strategies has been to provide toolkits to OB/GYN physicians that include scripts and other information to help them. ACOG is also conducting a series of Webinars to inform OB/GYN physicians and their office personnel about Tdap recommendations. In addition, ACOG had an app that can be downloaded to Androids and iPhones to access the toolkits and Webinars.

Dr. Loehr (AAFP) reported that the AAFP is also trying to disseminate this information to as many family physicians as possible, so he was disappointed to hear that the coverage rate is only 15%.

Dr. Baker (IDSA) congratulated ACOG for doing a wonderful job in collaboration with CDC on education of HCP and pregnant women. However, reimbursement continues to be a barrier. For example, although California delivers a lot of babies, Tdap is not paid for by California Medicaid. Aside from the problems of purchasing the vaccine, storing it in the office, and other practical barriers, administering this vaccine prevents death. The UK has demonstrated that there is over 90% vaccine effectiveness when the vaccine is given to pregnant women in the third trimester. That is a tremendous benefit. Tdap reimbursement in the US for pregnant women is an important issue for well-meaning HCP who know it is recommended for this

population and have the ability to administer the vaccine, but are not reimbursed for it. Dr. Baker also applauded the increased safety monitoring for pregnant women.

Regarding California Medicaid coverage of Tdap, Ms. Hance (CMS) explained that due to the way the program exists currently, there is some disconnect in coverage of vaccines in general for adults. CMS is aware of this. Under the Medicaid expansion, all of the ACIP-recommended adult vaccines are covered. This includes women under 21 years of age who are pregnant who would be covered through the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) in the traditional Medicaid program. The gap lies with people who are in the traditional Medicaid program who do not have coverage through the Medicaid expansion. This gap was created with the ACA and CMS is aware of it. Legislative change will be necessary to address this gap, and this is on CMS's agenda and has been included in a couple of bills. The Medicaid program is a state option, so states can choose to cover or not cover vaccines. However, this is not all or nothing. Some states have chosen to cover some vaccines even if they do not cover Tdap. The hope is to achieve across-the-board coverage at some point.

Dr. Harrison asked for a report from the manufacturers on development of next generation vaccines.

Dr. Decker (Sanofi Pasteur) responded that manufacturers are assessing what can be done about improved pertussis vaccines, but the structural barriers are formidable. For example, he does not believe anyone has figured out a way to license a new pertussis vaccine—certainly not a new infant pertussis vaccine. The regulatory authorities would require an endpoint clinical trial. There is no accepted generic correlate of immunity for pertussis. It is vaccine-specific. Every pertussis vaccine licensed throughout the world was licensed on the basis of a specific efficacy trial. Those cannot be conducted in a practical way any longer because there is no place in the world that does not recommend pertussis vaccine. The efficacy of acellular pertussis vaccine in the primary series is 90%, so the sample size required to meet non-inferiority criteria is larger than the population of a single country. These problems must be figured out. In addition, although some work is being done on perfecting animal models, no animal model has proven to be a valid correlate to the human response. He suggested doing the best they could with the available vaccines, because he could not predict when there would be new ones.

Dr. Phil Hosbach (Sanofi Pasteur) said he was heartened to see the focus on improving adult coverage, including HCP. Raising the immunization rates in pregnant women from 15% is going to take a lot of work. Focusing on maternal immunization is targeted and appears to be very effective, but it is going to take time to reach 80% to 90% coverage. In the meantime, he suggested using the tools available to ensure that there is a focus on immunizing those who take care of infants as well, including fathers, grandparents, HCP, and daycare providers.

Dr. Leonard Friedland (GSK) reported that GSK's research and development group is assessing how new and potentially improved pertussis vaccines can be developed. Meanwhile, their focus is on doing what they can to help the healthcare community understand how to improve adult and elderly coverage of Tdap vaccines. They are also committed to generating data regarding maternity immunization with Tdap vaccine so that groups such as ACIP can make informed decisions about how to use these vaccines safely and effectively in pregnant women.

Dr. Kempe, who is an Implementation Scientist, emphasized that there are major implementation issues for OB/GYNs in addition to payment concerns. These practitioners are beginning to deliver a lot of vaccines, health system development and other issues must be addressed. ACOG has recently agreed to conduct a survey, that will be funded by CDC, to assess the processes that are lacking, define what OB/GYNs need to deliver vaccine more effectively, and determine what types of systems can be adopted from other specialties.

Ms. Pellegrini pointed out that a recent NVAC report on maternal immunization beautifully encapsulated the challenges for OB/GYNs who have not had a long history of considering themselves to be vaccinators. A substantial initial investment is required in the equipment and vaccine itself. There is also a tremendous learning curve, and there are shortage issues. This is a daunting prospect for many practices, so she emphasized the importance of helping them address the obstacles.

Ms. Amy Middleman (SAHM) asked whether the WG had considered making the 10-year booster dose recommendation to be Tdap rather than Td. This would be beneficial in terms of stocking, doses, physician implementation, and ease of recommendations.

Dr. Liang replied that the WG has been discussing a change from decennial Td to decennial Tdap, but by adding a second dose. Because Tdap is only licensed for a single dose, the guidance from ACIP in January 2013 was to consider adding a second dose and not expanding it to a decennial Tdap. The conclusion for the second dose for the general population was not to make any changes. No changes are being made for HCP recommendation either.

In thinking about vaccinating mothers during each pregnancy, Dr. Baker (IDSA) asked CDC's position on revaccinating the mother's cocoon members during her successive pregnancies.

Dr. Liang responded that the WG has been discussing this and plans to present on this topic during the February 2015 ACIP meeting. When CDC receives calls about this, the agency's current guidance is that because this vaccine is licensed for a single dose, all family members should be up-to-date with their Tdap vaccination.

General Recommendations

Introduction

Dr. Marietta Vázquez Chair, ACIP General Recommendations Work Group

Dr. Vazquez reminded everyone that the General Recommendations document is published in the *Morbidity and Mortality Weekly Report (MMWR)* every 3 to 5 years, and addresses a broad range of clinical practice issues that are relevant to all vaccines as opposed to the vaccine-specific publications. The General Recommendations are intended to address topics that cannot be attributed to a single vaccine, but that are germane to the practice of immunization in general. A number of topics have been or are being revised, including the following:

- Timing and Spacing of Immunobiologics
- Contraindications and Precautions
- Preventing and Managing Adverse Reactions
- Reporting Adverse Events After Vaccination
- Vaccine Administration
- Storage and Handling of Immunobiologics
- Altered Immunocompetence
- Special Situations
- Vaccination Records
- Vaccination Programs
- Vaccine Information Sources

As a reminder, content already viewed and discussed by ACIP including timing and spacing of immunobiologics and contraindications during the February 2013 meeting, contraindications and precautions during the February 2013 meeting, preventing and managing adverse reactions during the June 2013 meeting, vaccine administration during the October 2013 meeting, and vaccine storage and handling during the February 2014. Because a vote is necessary for CDC clearance and posting, the plan for this session was to vote on the first half of the document.

The purpose of this session was to review changes that have occurred since ACIP last discussed the document so that a vote could be taken. Major revisions were made in the following four areas, which were discussed during this session:

- Timing and spacing (febrile seizures and simultaneous vaccination)
- Contraindications and precautions (vaccination and anesthesia/surgery/hospitalization)
- Vaccine Administration (vaccine preparation and timely disposal)
- Vaccine Administration (clinical implications of non-standard vaccination practices)

The *Vaccine Information Sources* section was also discussed during this session, but was not included in the vote for the October 2014 ACIP meeting. It will be included for the vote on the second half of the document during the February 2015 ACIP meeting.

Timing and Spacing, Contraindications and Precautions, Vaccine Administration

Andrew Kroger, MD, MPH

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Kroger reiterated that the content to be discussed during this session was presented to ACIP in previous meetings throughout the past year. He presented brief background information for each of the four major topics to be addressed during this session, discussed what has occurred since the information was last presented, and showed relevant content. For each of these topics, he referred to the page and line numbers in the draft statement provided to ACIP members.

Information regarding the subtopic of *Febrile Seizures and Simultaneous Vaccination*, which falls under the section of the General Recommendations titled *Timing and Spacing of Immunobiologics* was presented to ACIP in February 2013, and new data were presented by ISO in June 2014. In 2010, there were reports of an increase in febrile seizures following the use of AFLURIA[®] vaccine in the Southern Hemisphere at 9 per 1000 doses in children 6 months

through 4 years of age, as well as high rates of fever in children 5 through 8 years of age. Follow-up safety surveillance by ISO detected increased rates of febrile seizures in children 12 months through 23 months of age receiving simultaneous vaccination with IIV and PCV13. These data were presented to ACIP in February 2011, which was about one month following the last iteration of the entire General Recommendations document was published. Information has been published in subsequent ACIP influenza-specific vaccine statements.

Language was added to the ACIP document to accommodate recognition of attributable risk of febrile seizures with simultaneous vaccination of IIV and PCV13. The language proposed during the February 2013 meeting reads as follows:

“During the 2010-2011 influenza season, surveillance systems detected safety signals for febrile seizures in young children following TIV and PCV13 vaccines. CDC studied the healthcare visit records of more than 200,000 vaccinated children 6 months through 59 months of age through the Vaccine Safety Datalink Project during the 2010-2011 influenza season. The analyses found that febrile seizures following TIV and PCV13 vaccines given to this age group were rare but did occur at higher than expected rates. The risk for febrile seizures peaked in children age 16 months and were more common when the two vaccines were given during the same healthcare visit. In this group, about one additional febrile seizure occurred among every 2,200 children vaccinated. After assessing benefits and risks, ACIP continues to recommend that TIV and PCV13 be given concomitantly if both are recommended (Leroy Z, Vaccine 2012).” [PAGE 5, LINE 18]

Since February 2013 when that language was presented, additional information has been presented to ACIP with a number of conclusions to the data. For the 2012-2013 and 2013-2014 seasons, no febrile seizure signal for IIV was observed with the formulation change. The VSD found persistence from 2010-2011 to 2011-2012 when the formulation of IIV remained the same. A CISA study found a higher rate of fever. While they did not assess febrile seizure, fever with simultaneous vaccination of IIV and PCV13, adjusted for DTaP vaccination, was evaluated. Most recently, additional VSD and Pregnancy Risk Assessment Monitoring System Post Licensure Rapid Immunization Safety Monitoring (PRISM) analyses found that increased risk of febrile seizures is not an independent effect of IIV. These data were presented to ACIP during the February 2014 meeting. Additional VSD and PRISM studies were split on whether there is an effect of PCV13 or DTaP on the risk of febrile seizures with simultaneous vaccination with IIV. In the VSD study, the highest risk was seen with all three vaccines administered simultaneously (PCV13, IIV, and DTaP). The attributable risk was 38 febrile seizures per 100,000 persons vaccinated. The PRISM study found no increased risk with TIV plus PCV13. ISO reviewed these data and recommended no change to the language presented in February 2013. At issue is the fact that these vaccines are recommended to prevent disease. Risk of disease is high, while febrile seizures are benign. Hence, the decision not to recommend withholding these vaccines and to administer them simultaneously if they are recommended.

The next topic, *Vaccination During Anesthesia/Surgery/Hospitalization*, is the *Contraindications and Precautions* section of the document. This is placed in this section because these represent circumstances in which a provider must decide whether to completely withhold a dose of vaccine or wait to give it based on the clinical conditions of the recipient. Information on this topic was presented to ACIP in 2013. A contraindication means that a vaccine should be withheld for individuals with certain conditions, while a precaution is a condition in a vaccine recipient that permits the provider to conduct a risk/benefit analysis to decide to whether to wait

to give a vaccine or withhold it. An example of a precaution would be a situation in which vaccination can be deferred if someone is acutely, moderately, or severely ill. The issue of vaccination during hospitalization is also relevant. CMS uses as a performance measure the offering of IIV to patients who are hospitalized with pneumonia. The reason this issue first arose for general recommendations is that CDC was contacted by an Australian pediatrician in December 2010 to inquire about the issue of deferring elective surgery when a vaccine has already been given, and whether there should be an interval.

Prior to February 2013, the WG assessed the evidence from 20 sources that discussed hospitalization, surgery, and anesthesia. Of these studies, 15 addressed immune response, but only 5 of those addressed immune response following a dose of vaccine. These 5 studies were comprised of 1 systematic review, 1 editorial, and 3 letters. The remaining 15 studies that evaluated the immune response during hospitalization, surgery, or anesthesia were inconsistent. Of these, 11 studies assessed specific cell types (antibodies versus lymphocytes). Of those 11 studies, the variation was significant. Some showed levels increasing for one type and decreasing for others. There was also a lot of inconsistency in 6 papers that specifically assessed infants and children. Some of these studies showed increases in the immune response during anesthesia, hospitalization and surgery in infants and toddlers. Some showed decreases in the immune response in infants and toddlers. Others showed differences between toddlers and infants in the same paper. The evidence summary was presented to ACIP during the February 2013 meeting. That summary concluded that most studies that have explored the effect of surgery or anesthesia on the immune system were observational, included only infants and children, and were small and indirect, in that they did not look at the immune effect on the response to vaccination specifically. They do not provide convincing evidence that recent anesthesia or surgery significantly affect the response to vaccines. Along with this summary, which appears in the document, is the following statement:

“The optimal time for vaccination may be hospital discharge to avoid superimposing any vaccine-induced adverse effects on underlying conditions or avoid confusion in determining the etiology for conditions that occur or are exacerbated during the hospitalization. For patients who are deemed moderately or severely ill at the time of discharge, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients’ clinical symptoms have improved.”

This statement was presented to ACIP in February 2013. Based on the discussion pertaining to this language, specifically in the context of influenza vaccine, the General Recommendations Work Group (GRWG) revised the language of the statement to emphasize “during the hospitalization or at discharge.” The revisions are as follows:

~~“The optimal time for vaccination may be hospital discharge to avoid superimposing any vaccine-induced adverse effects on underlying conditions or avoid confusion in determining the etiology for conditions that occur or are exacerbated during the hospitalization. For patients who are deemed moderately or severely ill at the time of discharge, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients’ clinical symptoms have improved.”~~ Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients’ clinical symptoms have improved.” [PAGE 20, LINE 26]

The change in this language better ties the concept into a precaution, in that the language is maintained for patients deemed moderately or severely ill throughout the hospitalization. In those circumstances, it makes sense to vaccinate near the end of the hospitalization as opposed to the beginning. The WG wanted to include information that would allow providers to administer vaccines at other times. Regarding the context of elective surgery following a dose of vaccine, Dr. Kroger reminded ACIP of language in the document that was added since 2011 that was presented in February 2013 that states a new criteria for labeling a situation a precaution, shown as follows:

“A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction, might cause diagnostic confusion or that might compromise the ability of the vaccine to produce immunity.” [PAGE 19, LINE 19]

The only change is the underlined content, and is in the same section of the document that precedes administration during hospitalization, anesthesia, and surgery. This provides an option for providers who are concerned about elective surgery, or concern in hospitalized patients about the confusion of a post-surgical fever and the fact that giving a vaccine dose might cause diagnostic confusion.

Content for *Vaccine Administration: Safe Injection Practices*, was presented to ACIP in October 2013. At the time, the discussion regarded preparation and timely disposal and multi-dose vials. CDC's Vaccine Safe Injection Practices program had specific language on its website, some of which is still there, which includes specific information regarding reinsertion of used needles in multi-dose vials. The GRWG was troubled by situations in which multi-dose vials can be opened in proximity to the patient. The CDC Vaccine Safe Injection Practices program is part of a WG tasked to address such administration issues. They do impact the ACIP General Recommendations, and they have pushed content that has cleared CDC with regard to this topic. The presentation of this content during the October 2013 meeting generated a lot of discussion. The following is the language taken verbatim from the CDC's Vaccine Safe Injection Practices program at the following link:

http://www.cdc.gov/injectionsafety/providers/provider_faqs_multivials.html

“Vaccines should be drawn up in a designated clean medication area that is not adjacent to areas where potentially contaminated items are placed. Multi-dose vials to be used for more than one patient should not be kept or accessed in the immediate patient treatment area. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment that could then lead to infections in subsequent patients. If a multi-dose vial enters the immediate patient treatment area, it should be discarded after use.”

There was discussion in October 2013 about the context of community vaccination clinics, mass vaccination clinics, and satellite clinics in terms of how this could be done if the space to vaccinate is small. Those at CDC who are involved with the Vaccine Administration WG discussed this and determined that a lot of this language, though not all of it, is posted on CDC's website already. Therefore, the GRWG proposed to revise the language as follows:

“Multi-dose vials to be used for more than one patient should not be kept or accessed in the immediate patient treatment area. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment that could then lead to infections in subsequent patients. ~~If a multi-dose vial enters the immediate patient treatment area, it should be discarded after use.~~” [PAGE 34, LINE 26]

Content for *Vaccine Administration: Clinical Implications of Non-Standard Vaccination Practices* was also discussed with ACIP in October 2013. This pertains to the route of administration, and much of this stems from a different section of the General Recommendations that discusses providers treating patients with hemophilia. There is language in the recommendations, that there is no intent to revise, which indicates that for vaccines approved for intramuscular administration, providers can use the intramuscular route for patients with hemophilia if the bleeding risk is acceptable. Some providers might take this to be a license to administer vaccines subcutaneously. The question is: Should such doses count? The challenge is that the evidence varies by vaccine. The General Recommendations do state that vaccines approved for subcutaneous use only may be given IM and will be counted.

Hepatitis B vaccine is approved for IM use. Data have been published by Shaw, Redfield, and Coleman showing that immunogenicity is lower if administered in the gluteus, presumably into subcutaneous deep fat, or intradermally. Newer studies show comparable immunogenicity when comparing IM versus subcutaneous vaccine specifically performed in hemophiliacs receiving hepatitis B immune globulin (HBIG) vaccine and who are specifically at risk for infection by hepatitis B virus (HBV) [Shaw F, Jr., et al, *Vaccine* 1989;7:425—30; Redfield RR, et al, *JAMA* 1985;254:3203—6; Coleman PJ, et al, *Vaccine* 1991;9:723—7; Gazengel C, et al. *Scand J Haematol*, 1984; Janco RL. *J Pediatr*, 1985; Zanetti AR, et al. *Am J Hematol*, 1986; Hedner U, et al. *Scand J Haematol*, 1984].

These available data limit the evidence for immunogenicity. Patients may already have been exposed to the virus by virtue of their risk. They may have received HBIG. However, the studies do not tease out all of the possibilities. Therefore, the WG basically concluded in October of 2013 that the recommendation should be maintained to repeat doses of hepatitis B vaccine given subcutaneously. There are some ongoing studies, but the current plan is to continue to recommend repeating doses of this vaccine given subcutaneously.

Rabies vaccine is also approved for IM. While an intradermal vaccination is used internationally, it is not used in the US. The current recommendation is to repeat doses administered in the gluteus, presumably into subcutaneous deep fat. The WG does not suggest any revisions to that recommendation.

HPV vaccine is approved for IM injection. There are no data to indicate reduced immunogenicity or effectiveness if administered by another route. The general practice is to recommend repeat dosing if administered subcutaneous, which is recommended on the basis of expert opinion and licensure alone.

Meningococcal conjugate vaccine is approved for IM administration. Polysaccharide vaccine (MPSV4) is approved for subcutaneous administration. CDC assessed the data for subcutaneous administration of MenACWY and found the doses to be immunogenic. Of the 38 subjects who received subcutaneous administration, 36 had protective titers. Therefore, CDC does not recommend repeating these doses [CDC. Inadvertent misadministration of meningococcal conjugate vaccine—United States, June-August 2005. *MMWR* 2006;55:101-7].

Hepatitis A vaccine (HAV) is recommended for IM administration. There is a paper that discusses comparable immunogenicity found in children with hemophilia when administered HepA vaccine either IM or subcutaneously. Seroconversion was comparable. The paper did not define a cutoff, but did show significant differences in the GMTs, but the authors concluded that there is not an appreciable difference in immunogenicity when HepA vaccine is administered subcutaneously [Ragni MV, et. Al, *Hemophilia*, 2000]. During the October 2013 ACIP meeting, HAV was added to MCV4 for vaccine for which ACIP does not recommend repeating the dose.

Haemophilus influenzae Type b (Hib) vaccine was not discussed during the October 2013 ACIP meeting. It is approved for IM administration. There are data to suggest a dose of Hib vaccine administered subcutaneously can be counted. A study by Christenson was published in the *Journal of Infectious Diseases* in 1992 of 20 splenectomized children, with one hemophiliac child who received the dose subcutaneously. Immunogenicity was comparable. On this basis, Hib was added to the list of vaccine for which ACIP does not recommend repeating the dose. [PAGE 44, LINE 5]

It is important to determine whether it is possible to generalize vaccines when the weight of the evidence available differs for various vaccines. Doses are validated in the current draft with no need to repeat if given subcutaneously, even though the evidence is weak, for HepA, Hib, and meningococcal conjugate vaccine. Doses are invalidate, supported by the evidence, which also is weak for HepB and rabies vaccines. Doses are also invalidate that are supported by the FDA package insert only for HPV vaccine. There is no guidance for other vaccines recommended to be administered IM, for example DTaP and meningococcal conjugate vaccine. Dr. Kroger developed the following proposed language, which he shared with the GRWG:

“DTaP and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP and PCV13, there is no evidence to support repeating doses of these vaccines if given subcutaneously. Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by-case basis.”

The second half of the document, which will be voted on in February 2015, contains a short section on vaccine information sources that has not yet been presented to ACIP. This section contains a listing of organizations with websites and contact information, and is the last section of the revised document to be reviewed by ACIP. This section will be voted on with the other remaining topics during the February 2015 meeting. The following organizations are listed in this section:

- CDC-INFO Contact Center
- CDC’s National Center for Immunization and Respiratory Diseases
- Morbidity and Mortality Weekly Report (MMWR)*
- American Academy of Pediatrics (AAP)

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- Immunization Action Coalition (IAC)
- National Network for Immunization Information (NNII)
- Vaccine Education Center (VEC)
- Institute for Vaccine Safety (IVS)
- Group on Immunization Education – Society for Teachers of Family Medicine (GIE-STFM)
- State and Local Health Departments

In conclusion, Dr. Kroger indicated that ACIP members have seen the draft document and have had an opportunity to weigh in on certain topics other than the ones presented during this session. Six of the members replied, three of whom indicated that they identified no issues and three of whom made specific comments pertaining to the following:

- Timing and Spacing, and Tables: Update TIV to IIV, depending on intent. Dr. Kroger noted that IIV is a general abbreviation that will be taken by providers as inclusive of IIV3, IIV4, CCIV, and all IV3. The General Recommendations discuss inactivated vaccines versus live vaccines.
- Timing and Spacing: Cross-reference live vaccines having a potential suppressive effect on the response to tuberculin skin tests and Interferon Gamma Release Assay tests for latent tuberculosis infection (LTBI). This is already in the text, but needs referencing in other parts of the document, namely the tables.
- Timing and Spacing: Change the language to de-emphasize blunting effect of PPSV23 on PCV13. Instead, emphasize the positive priming effect of PCV13 on PPSV23. The document will go through CDC clearance, so Dr. Kroger envisioned using language from the pneumococcal vaccine-specific statement that was recently published.

While these changes were not reflected in the draft presented during this session, Dr. Kroger will ensure that these changes are made.

Discussion Points

Dr. Kempe thought it was fair to say that there are no data regarding Hib, given that there was only 1 child in the study assessed. She also asked how many subjects were in the HepA study.

Dr. Kroger replied that the HepA study involved 45 subjects who received the vaccination subcutaneously, all of whom were hepatitis A negative at baseline.

In terms of vaccine given subcutaneously rather than IM, if a vaccine is one for which there is a serologic definition of protection, such as hepatitis A or hepatitis B surface antibody, Dr. Rubin wondered whether language should be included for that as evidence of immunity.

Dr. Fryhofer (AMA/ACP) expressed her appreciation for the brief explanation on page 1 of the difference between conjugate and polysaccharide vaccines, which should be beneficial to practitioners. On page 6 and 12, there is a warning not to give the MCV4-D (Menactra[®]) vaccine together with PCV13. She did not believe a lot of practitioners realized that. The patients to which that would apply are those with anatomic or functional asplenia, and it would be helpful to include this on the adult schedule. The abbreviation used, MCV4-D, is now

MenACWY on the adult schedule. All of the acronyms are very confusing for practitioners, so she suggested including more acronyms that mean the same thing.

Dr. Byington (AAP) reported that AAP is receiving a lot of questions from anesthesiologists about delaying elective surgery post-immunization. She asked whether there is specific language stating that this does not need to be done.

Dr. Kroger responded that language will be included that vaccine can be administered at any time during the hospitalization. There is discussion regarding the strength of the evidence, but it will probably not be as prescriptive as Dr. Byington suggested based on the evidence.

Dr. Byington (AAP) clarified that the questions AAP is getting regard immunizations that have already occurred in the outpatient setting, and now the child is presenting for an elective procedure. Anesthesiologists are turning them away for 10 days to two weeks following immunization in the outpatient setting. That seems to be a misinterpretation of the recommendations.

Dr. Kroger said the issue regards how strongly that statement can be made. The WG is not going as far as to say that there is no need to wait an interval. There are no plans to include that language directly in the document, but he is open to further discussion for potentially including it.

Dr. Temte added that many children who have scheduled surgery are presenting to pediatricians or other practitioners for a pre-operative examination. Technically, that has to be 30 days before the procedure. Many practitioners use that opportunity to catch up on vaccination, so that is a very salient point. Also, a number of surgeons are reluctant to vaccinate prior to discharge because of the likelihood of a fever. People do not stay in the hospital as long as they used to. They are being sent home with explicit instructions to call back if there is a fever. They are unlikely to reach the person who discharged them, and often that results in an emergency department (ED) visit with labs, radiographs, et cetera. This is not a minor issue.

Ms. Pellegrini pointed out that while the recommendation regarding subcutaneous administration of DTaP and PCV13 stated that “there is no evidence to support repeating doses of these vaccines if given subcutaneously,” there is also no evidence to say doses should not be repeated. She suggested stating this more neutrally. She wondered if there was any new evidence anticipated in the future that would offer providers more constructive guidance.

Dr. Kroger replied that what is currently happening is that in the context of one patient, it is recommended to repeat the dose. In contexts where there may be hundreds or thousands of patients, that becomes more problematic and raises the question of whether it is even possible to generalize on the issue at all. If not, the argument could be made to take this out and not even have any discussion about it in the General Recommendations on immunization, which is a viable option. If it is possible to generalize, then something has to be said for this circumstance. The language could be stated more neutrally.

Dr. Baker (IDSA) pointed out that most children have surgical procedures as outpatients. She understands the problem of no evidence. ACIP did not have much evidence when they recommended immunizing pregnant women. She wondered whether they could say something like, “there is no contraindication.” She asked what the AAP recommends in the Red Book.

Dr. Kroger responded that with the proposed language, that is defined as a precaution. In the implementation of these recommendations, stating that it is not a contraindication would be a valid statement to make. It would be possible to include that language in the document.

Dr. Kimberlin (AAP) added that the only place the word “anesthesia” or “anesthetic” appears in Section 1 of the Red Book pertains to topical anesthesia to numb a site before an injection.

Dr. Baker suggested considering the addition of the information pertaining to surgery to the Red Book before publication.

Dr. Rubin’s institution has made a general suggestion that inactivated vaccines should not be given within 2 days prior to surgery and live vaccines within 14 days prior to surgery, but if those vaccines are inadvertently given, there is no reason to cancel surgery.

Dr. Temte emphasized that there would never be sufficient evidence one way or the other; therefore, expert opinion is reasonable in this situation. If they wait, this document will be incomplete for years.

It seemed to Dr. Rubin that if a vaccine approved for IM use is given by the wrong route, unless there is evidence that giving the vaccine subcutaneously generates adequate antibody, that vaccine should not receive a pass. The vaccine should be repeated as a policy.

Dr. Temte asked whether the members would be more comfortable keeping Hib as a repeat given the importance of this vaccine in terms of child health, given that the evidence is very thin.

Dr. Kroger said that they could do that.

With no other comments or questions raised, Dr. Temte asked whether the ACIP members felt that they could move forward with a vote at this time.

Dr. Vazquez put forth a motion to approve the recommendations as presented, with the changes discussed. Dr. Bocchini seconded the motion.

Dr. Bennett said she was anxious about voting without seeing the revised version, given the number of changes suggested during the discussion.

Dr. Temte requested that the revisions be made and presented to the group during the Unfinished Business session the next morning. Others agreed that this would be beneficial and acceptable, given that it was not entirely clear what they were voting on.

Dr. Vazquez withdrew the motion, with stipulation that during the Unfinished Business section the next day, the revised language would be submitted for a vote.

Revised Language for the Vote

Andrew Kroger, MD, MPH National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention

At the request of the ACIP members, Dr. Kroger incorporated the discussion points raised during the General Recommendations session during the first day of the meeting and presented the revised language during the Unfinished Business session the next morning. This information is included with the information from the General Recommendations session for continuity and ease of reading.

Dr. Kroger reminded everyone that the following issues related to wording that needed revision:

- ❑ Wording presented to ACIP on 10/29/14 that needed some revision
 - 1. Contraindications and Precautions
 - Vaccination during anesthesia/surgery/hospitalization
 - 2. Vaccine Administration
 - Clinical Implications of Non-Standard Vaccination Practices
 - 2a) Statement regarding subcutaneous administration of vaccines approved by the intramuscular route for which there are no data
 - 2b) Inclusion of Hib vaccine in above statement
- ❑ Revision shared from ACIP regarding simultaneous vaccination of PCV13 and PPSV23
 - 1. Revision to draft language to separate these vaccines (not presented to ACIP on 10/29/14, but shared with ACIP on 10/10/14)

In terms of *Contraindications and Precautions*, Dr. Kroger previously showed the evidence summary based on the lack of data regarding whether an interval is needed before or after vaccines and surgery/anesthesia. The available evidence includes observational and indirect studies and do not assess the immune effect on the response to vaccination specifically, or at least the vast majority of studies do not do that and do not provide convincing evidence that recent anesthesia or surgery significantly affect the response to vaccine. He did not propose a change to that or to the action statement.

ACIP concerns from the previous day focused on the issue of patients recently vaccinated who may be scheduled for elective surgery. It was noted that some providers already use intervals. However, there must be some flexibility as to the timing of when to vaccinate. Concerns were also expressed by liaison members from the AAP and IDSA regarding the current language in the document defining hospitalization/surgery/anesthesia as a precaution, given that this might lead to withholding vaccines that can be protective by preventing disease in someone with upcoming surgery. Concerns may be different for different vaccines. Guidance is needed, but it cannot be too prohibitive. The proposal was to connect the evidence summary and the action statement with a bridging statement about the fact that current, recent, or upcoming anesthesia/surgery/hospitalization is not a contraindication to vaccination. The full statement would read as follows:

“Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients’ clinical symptoms have improved. Current, recent, or upcoming anesthesia/surgery/hospitalization is not a contraindication to vaccination.

In terms of *Vaccine Administration: Clinical Implications of Non-Standard Vaccination Practices*, ACIP members expressed several concerns related to the statements regarding counting or not counting a dose of vaccine given subcutaneously. The current language places the burden on the evidence to demonstrate that doses of DTaP and PCV13 administered subcutaneously need to be repeated. The burden cannot be placed on the evidence to demonstrate that doses need to be counted generally, because there is no such evidence for HPV vaccine. Hib vaccine cannot be grouped with Hepatitis A vaccine and MCV4/MenACWY since the level of evidence is not met to avoid grouping Hib with DTaP and PCV13. All of this was in the context of providing more neutral language that does not put forward a specific action step. The revised language would read as follows:

“DTaP, Hib, and PCV13, like all other vaccines approved for intramuscular use, should be administered by the intramuscular route. However, for DTaP, Hib, and PCV13, there is no evidence related to immunogenicity of these three vaccines given subcutaneously. Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by-case basis.”

Regarding *Timing and Spacing of Immunobiologics: Simultaneous Administration of PCV13 and PPSV23*, the draft document was sent to ACIP on October 10, 2014. A comment was received on October 20, 2014 to emphasize the positive priming effect of PCV13, as opposed to any effect of PPSV23 to blunt the immune response to subsequent doses. The ACIP membership wanted to see this change before voting. The GRWG proposal is to adopt language from the Pneumococcal Vaccine Specific Statement from 2014 [*MMWR*. 2014;63 (37);822-825]. The language will need to flow with the rest of the General Recommendations document. The following language was proposed, taken almost completely from the pneumococcal-specific statement:

“In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. Immunogenicity studies evaluating responses to PCV7 and PPSV23 administered in series showed a better immune response when PCV7 was administered first. An evaluation of immune response after a second pneumococcal vaccination administered 1 year after the initial study doses showed that subjects who received PPSV23 as the initial study dose had lower antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose followed by a dose of PPSV23, regardless of the level of the initial response to PPSV23. PCV13 should be administered first. If PPSV23 has been administered first, PCV13 should be administered no earlier than one year later.”

Discussion Points

Dr. Temte thanked Dr. Kroger for his hard work in putting this presentation together overnight.

For the PCV13/PPSV23 statement, Dr. Belongia suggested placing the action item at the beginning. The statement would then read:

“In patients recommended for both PCV13 and PPSV23, the two vaccines should not be administered simultaneously. PCV13 should be administered first. If PPSV23 has been administered first, PCV13 should be administered no earlier than one year later. Immunogenicity studies evaluating responses to PCV7 and PPSV23 administered in series showed a better immune response when PCV7 was administered first. An evaluation of immune response after a second pneumococcal vaccination administered 1 year after the initial study doses showed that subjects who received PPSV23 as the initial study dose had lower antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose followed by a dose of PPSV23, regardless of the level of the initial response to PPSV23.”

Dr. Kroger indicated that he would make this revision.

Dr. Reingold said that while he has not been a clinician for a long time, he did not know what he would do with the last sentence in the statement pertaining to DTaP, Hib, and PCV13 reading, “Providers should address circumstances in which dose(s) of these vaccines have been administered subcutaneously on a case-by-case basis.”

Dr. Temte said that in all of his years of practice, he was not aware of any of his patients ever being administered an IM in a subcutaneous route. If it did occur, it would depend on the situation. If it is a repeat immunization for which a patient has already been primed, he would not be concerned. However, he feels strongly that an initial Hib vaccine needs to be administered appropriately. This is a situation in which there is no evidence one way or the other, and it is unlikely that new evidence will be forthcoming. In this situation, a “fuzzy” statement may be acceptable.

Dr. Loehr (AAFP) agreed that a “fuzzy” statement was appropriate due to lack of evidence either way; however, he suggested including language to articulate specifically that there is no evidence one way or the other.

Ms. Groom (IHS) noted that previously, it was clear that these three vaccines probably did not need to be repeated. However, the proposed wording seemed unclear about whether to repeat doses. Just stating that there is no evidence will not give the clinician an idea about whether to repeat doses.

Dr. Kroger said that from an implementation standpoint, when these vaccines are given, clinicians have been instructed to repeat a dose if it is for a single patient. The issue is when many doses are given. Hence, the case-by-case basis issue for implementation.

Dr. Kempe’s recollection was that this is in the context of ACIP already saying there is some evidence for a few vaccines. The “however” in the statement seemed out of place. This would be saying that secondarily, for these three vaccines, there is no evidence.

Dr. Kroger replied that there is adequate evidence for meningococcal and HepA vaccines.

Dr. Kempe observed that in that context, the statement made more sense and says what it needs to say—there is no evidence.

Vote: General Recommendations

Dr. Vazquez made a motion to accept the language as proposed. Dr. Bocchini seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. Two members were absent. The disposition of the vote was as follows:

13 Favored: Bennett, Belongia, Bocchini, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A
2 Absent: Campos-Outcalt, Harriman

Child/Adolescent Immunization Schedule

Introduction

Dr. José R Romero
ACIP Chair
Child/Adolescent Immunization Work Group

Dr. Romero introduced this session on behalf of Child/Adolescent Immunization WG. He reminded everyone that the schedule is presented for vote every fall, given that the ACIP's approval is necessary prior to publication of the schedule in January or February of the following year. ACIP's approval is also necessary before its partners AAP, AAFP, and ACOG review and approve the schedule. No new policy is established by the schedule; rather, it reflects a summary of published ACIP recommendations. These edits are intended to improve readability and utility of the schedule, and hence translate the respective ACIP recommendations into language that is easy to interpret for the busy provider.

This year, only a few vaccines' schedules require attention. Posted on the website available to ACIP members are the full set of footnotes; the catch-up schedule; and revised job aids for DTaP, Hib, and pneumococcal vaccines discussed during the last ACIP meeting. These latter documents will be published by CDC, and while they do not require ACIP's approval, the ACIP members were asked to review them in the next few weeks to assure they are consistent with the current Childhood/Adolescent Immunization Schedule. For the remainder of this presentation, Dr. Strikas discussed the proposed edits to some specific vaccine footnotes, as well as the Catch-up Table.

ActHIB®, PENTACEL®, or an unknown vaccine, which might be either of those. For an interval of 8 weeks between these doses, and to be the final dose in the series, the WG deleted what appeared unnecessary, stating “regardless of Hib vaccine used.” Also defined for children 12 through 59 months of age is that they must have received a second dose before age 15 months to allow completion of the series in 8 weeks’ time with one more dose. Some language was deleted in the last category to read “both doses were PRP-OMP vaccines” and again used “before the 1st birthday.”

In the Hib dose 3 to 4 column, because any child who received 3 doses of any Hib vaccine before 12 months of age should receive one more dose, the vaccines named in the strikeout section highlighted may be deleted, and the timing of receipt need only say it was before the 1st birthday. For pneumococcal conjugate vaccine, in the dose 1 to 2 column, minor wording changes are proposed, including “before the 1st birthday” rather than “younger than age 12 months” and insertion of the word “was” before “administered” in the second segment.

In the dose 2 to 3 column, language was modified at length to better adhere to the 2010 routine childhood recommendations: “Dose 3 should be given 4 weeks after dose 2 if the child is younger than 12 months, AND the previous dose was given before 7 months of age. Dose 3 as the final dose should be given 8 weeks after dose 2 if the previous dose (dose 2) was given between 7 and 11 months of age; this 3rd and final dose should be given at 12 months of age or older, OR the child is 12 months of age or older and received at least one of the two vaccine doses before age 12 months,” they can complete the series at that time.

In the Tdap section, wording was simplified again using “before the 1st birthday” rather than “younger than age 12 months” and unnecessary language was deleted where it is already defined that the Td or Tdap dose will be the final dose in the series. The last Td/Tdap edit was to say again in the dose 3 to dose 4 column “before the 1st birthday” rather than “younger than age 12 months.” Minimum age for dose 1 for hepatitis A, hepatitis B, polio, meningococcal, MMR, and varicella vaccines is not relevant in the catch-up schedule for children already 7 years of age, so these are indicated as “not applicable.” In the varicella section for children 7 years and older, “person is” was deleted for simplicity.

Here are the footnotes:

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years — United States, 2015

For further guidance on the use of the vaccines mentioned below, see <http://www.cdc.gov/vaccines/imz/downloads.html>.

For vaccine recommendations for persons 19 years of age and older, see the adult immunization schedule.

Additional information:

- For recommendations and precautions to use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

Hepatitis B (HepB) vaccine (Immunovax age 6 years)

Immunovax (Immunovax age 6 years)

Additional information:

- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

Rotavirus (RV) vaccine (Immunovax age 6 years)

Immunovax (Immunovax age 6 years)

Additional information:

- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

For further guidance on the use of the vaccines mentioned below, see <http://www.cdc.gov/vaccines/imz/downloads.html>.

Hemophilus influenzae type b (Hib) conjugate vaccine (actHIB)

actHIB (actHIB age 6 years)

Additional information:

- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

Pneumococcal vaccines (actHIB)

actHIB (actHIB age 6 years)

Additional information:

- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

Poliovirus vaccine (IPV)

IPV (IPV age 6 years)

Additional information:

- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.
- For information on the use of a vaccine with additional information regarding the vaccine, vaccine providers should consult the relevant ACIP reference available online at <http://www.cdc.gov/vaccines/imz/downloads.html>.

<p>9. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)</p> <p>Routine vaccination</p> <p>Administer a dose of MMR vaccine at age 12 through 15 months and a second dose at age 4 through 6 years. The second dose may be administered at age 18 months to 2 years if the child has not received a second dose by age 4 years.</p> <p>Administer 1 dose of MMR vaccine to children aged 6 through 12 months before departure from the United States to international travel. These children should be vaccinated with 1 dose of MMR vaccine at the time of departure. If the child returns to the United States before the 12-month anniversary of the first dose, the second dose should be administered at age 12 months.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of MMR vaccine should be vaccinated at age 12 months. Children who have received 1 dose of MMR vaccine should be vaccinated at age 4 through 6 years.</p>	<p>Routine vaccination</p> <p>Administer a dose of MMR vaccine at age 11 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of MMR vaccine should be vaccinated at age 11 through 12 years. Children who have received 1 dose of MMR vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p>
<p>10. Varicella (VZV) vaccine. (Minimum age: 12 months)</p> <p>Routine vaccination</p> <p>Administer 1 dose of varicella vaccine at age 12 through 15 months and a second dose at age 4 through 6 years. The second dose may be administered at age 18 months to 2 years if the child has not received a second dose by age 4 years.</p> <p>Administer 1 dose of varicella vaccine to children aged 6 through 12 months before departure from the United States to international travel. These children should be vaccinated with 1 dose of varicella vaccine at the time of departure. If the child returns to the United States before the 12-month anniversary of the first dose, the second dose should be administered at age 12 months.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of varicella vaccine should be vaccinated at age 12 months. Children who have received 1 dose of varicella vaccine should be vaccinated at age 4 through 6 years.</p>	<p>Routine vaccination</p> <p>Administer 1 dose of varicella vaccine at age 11 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of varicella vaccine should be vaccinated at age 11 through 12 years. Children who have received 1 dose of varicella vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p>
<p>11. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)</p> <p>Routine vaccination</p> <p>Administer 1 dose of HepA vaccine at age 12 through 15 months and a second dose at age 4 through 6 years. The second dose may be administered at age 18 months to 2 years if the child has not received a second dose by age 4 years.</p> <p>Administer 1 dose of HepA vaccine to children aged 6 through 12 months before departure from the United States to international travel. These children should be vaccinated with 1 dose of HepA vaccine at the time of departure. If the child returns to the United States before the 12-month anniversary of the first dose, the second dose should be administered at age 12 months.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of HepA vaccine should be vaccinated at age 12 months. Children who have received 1 dose of HepA vaccine should be vaccinated at age 4 through 6 years.</p>	<p>Routine vaccination</p> <p>Administer 1 dose of HepA vaccine at age 11 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of HepA vaccine should be vaccinated at age 11 through 12 years. Children who have received 1 dose of HepA vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p>
<p>12. Human papillomavirus (HPV) vaccine. (Minimum age: 9 years for HPV2 (Cervarix) and HPV4 (Gardasil))</p> <p>Routine vaccination</p> <p>Administer 1 dose of HPV vaccine at age 9 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 9 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of HPV vaccine should be vaccinated at age 9 through 12 years. Children who have received 1 dose of HPV vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 9 through 12 years with high risk conditions, see below.</p>	<p>Routine vaccination</p> <p>Administer 1 dose of HPV vaccine at age 11 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of HPV vaccine should be vaccinated at age 11 through 12 years. Children who have received 1 dose of HPV vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p>
<p>13. Meningococcal conjugate vaccine. (Minimum age: 9 weeks for Hib Menveo [Menveo], Menveo for MenACWY (Menveo), 2 months for Hib Menveo [Menveo])</p> <p>Routine vaccination</p> <p>Administer 1 dose of Hib Menveo vaccine at age 9 weeks, with a booster dose at age 15 through 18 months. The second dose may be administered at age 18 months to 2 years if the child has not received a second dose by age 4 years.</p> <p>Administer 1 dose of Hib Menveo vaccine to children aged 6 through 12 months before departure from the United States to international travel. These children should be vaccinated with 1 dose of Hib Menveo vaccine at the time of departure. If the child returns to the United States before the 12-month anniversary of the first dose, the second dose should be administered at age 12 months.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of Hib Menveo vaccine should be vaccinated at age 9 weeks. Children who have received 1 dose of Hib Menveo vaccine should be vaccinated at age 15 through 18 months.</p>	<p>Routine vaccination</p> <p>Administer 1 dose of Hib Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p> <p>Catch-up vaccination</p> <p>Children who have not received 1 dose of Hib Menveo vaccine should be vaccinated at age 11 through 12 years. Children who have received 1 dose of Hib Menveo vaccine should be vaccinated at age 16 through 18 years with routine immunization or MMR infection should occur in a state primary care practice or in a state with high risk conditions. See below.</p> <p>For children aged 11 through 12 years with high risk conditions, see below.</p>

In footnote 3 for DTaP, language presently in the General Recommendations on Immunization was added, indicating children who had already received the 4th dose of DTaP at age 12 months can have the dose count if the dose followed the 3rd dose by at least 4 months. In footnote 6 for pneumococcal conjugate vaccine, language was added to follow more closely the 2010 recommendations for high risk children 2 to 5 years of age, that they should receive 1 dose of this vaccine if the child had received any incomplete series of pneumococcal conjugate vaccine, whether 7- or 13-valent, AND such children should receive 2 doses of PCV 13 if they had received fewer than 3 doses of any conjugate vaccine in the past. That is verbatim from the 2010 recommendations.

In the influenza footnote, the only changes were to update the dates for the 2014-2015 season, update the references, and to point to the relevant recommendations. The meningococcal footnote had more substantial editing to more clearly identify the appropriate dosing schedules for high risk infants and children for the three different vaccines. These were stratified by condition and by vaccine type. This footnote had not previously addressed use of Menveo[®] in children 7 months of age and older. For children with persistent complement component deficiencies, a similar re-structuring was written of the footnote that is stratified by vaccine type.

Regarding next steps, the WG will make revisions as necessary based on feedback from ACIP and CDC internal clearance, and will then send it to colleagues AAP, AAFP, and ACOG. The final edited copy will be sent to partner organizations for preparation of publication in their journals or their on-line publications by January 1, 2015. The hope is to publish the schedule on the website, with a notice in the *MMWR* in January or at the latest February 2015, as well as in publications in *Pediatrics* and *American Family Physician* no later than February 2015.

Discussion Points

Referring to tetanus/diphtheria dose 3 to 4, Dr. Loehr (AAFP) noted that the box is correct on the page that has the correction. However, on all of the other pages it says “if first dose of DTaP/DT was administered” and “if first dose of DTaP was administered.” This needs to be corrected on the final copy.

Ms. Groom (IHS) expressed gratitude for the changes to the Hib language, which she believes will be incredibly helpful.

Dr. Strikas acknowledged Elizabeth Briere and the WG's colleagues whom work on Hib regularly.

Dr. Pickering reminded the WG to use the word "through" rather than dashes for age ranges for clarity.

Dr. Strikas indicated that the WG would go through the document to ensure that all of dashes are changed.

Vote: Child/Adolescent Immunization Schedule

Dr. Rubin made a motion to approve the Child/Adolescent Immunization Schedule as proposed. Dr. Kempe seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. Two members were absent. The disposition of the vote was as follows:

13 Favored: Bennett, Belongia, Bocchini, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A
2 Absent: Campos-Outcalt, Harriman

Adult Immunization Schedule

Introduction

Dr. Laura Riley ACIP Chair, Adult Immunization Work Group

Dr. Riley reminded everyone that ACIP updates the adult immunization schedule each year. The schedule represents and summarizes existing ACIP policy. The WG meets monthly and engages in ongoing consultation with vaccine subject matter experts (SMEs) to recognize changes over time.

Updates on the pneumococcal vaccination recommendation were recently approved regarding policy changes from the additional ACIP meeting on August 13, 2015 and published in the *MMWR* on September 19, 2014. These were discussed in great detail by the WG. The 2014 Adult Immunization Schedule was also approved by the following:

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- American College of Obstetricians and Gynecologists (ACOG)
- American College of Nurse Midwives (ACNM)

Adult Immunization Communication Materials

Dr. Kristine Sheedy
Associate Director
Office of Health Communication Science
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

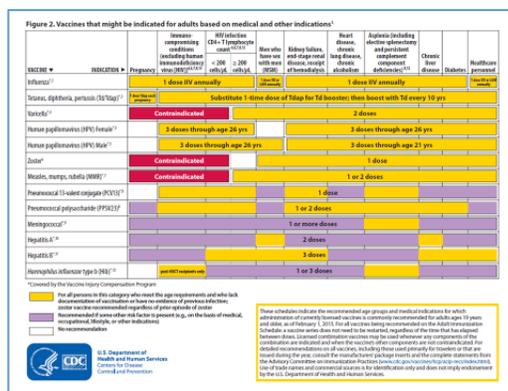
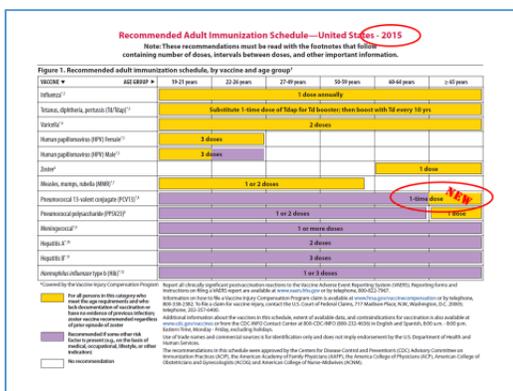
Dr. Sheedy called the ACIP members' attention to a folder of materials given to them, which included samples of some of the direct consumer and clinician adult immunization materials that have been developed. CDC is currently working with the IAC and Medscape to develop a series of features on adult immunization standards to cover assessment, recommendations, administration, referral, and documentation.

The assessment features are available on line, and the recommendation features should be available soon. This feature will include case examples with common questions from patients about various adult vaccines, and video vignettes modeling how to answer those questions clearly and succinctly. Some of the pieces are currently available in Spanish, and more pieces will be translated as well.

Adult Immunization Schedule 2015

Dr. David Kim
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In this presentation, Dr. Kim described the proposed changes to the 2015 Adult Immunization Schedule. Here are Figures 1 and 2:



The proposed changes for Figure 1 are to replace the purple bar (recommended if at risk) with a yellow bar (recommended) for PCV13 for adults age ≥65 years. For the Footnotes, the WG proposed to reformat the language from vaccine-focused to patient-focused based on a request to make the footnotes as user-friendly as possible. In the Contraindications Table, the WG proposed adding changes associated with LAIV.

The changes to Contraindications were based on the recent article titled, “Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014–15 Influenza Season” [*MMWR* 2014;63 (32):691-97]. Wording changes in Contraindications include the following:

- ❑ “Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, or to a previous dose of any influenza vaccine.”
- ❑ “In addition, ACIP recommends that LAIV not be used in the following populations
 - Pregnant women;
 - Immunosuppressed persons;
 - Persons with egg allergy;
 - Children aged 2 through 4 years who have asthma or who have had a wheezing episode within the last 12 months;
 - Persons who have taken influenza antiviral medications within the previous 48 hours. Avoid use of these antiviral drugs for 14 days after vaccination.”

Other changes in Contraindications and Precautions include change from the term “Contraindication” to “Precaution” for antiviral use within last 48 hours, and from “Precaution” to “Contraindication” for chronic health conditions.

Regarding the 2014 Adult Immunization Schedule for pneumococcal vaccination, there are footnotes for PCV13, PPSV23, and revaccination with PPSV23. Population groups were divided into two age categories: Age ≥ 19 years and Age ≥ 65 years of age.

The common feedback the WG receives from those within and outside of CDC is that the pneumococcal vaccine recommendations are complex. That complexity comes from the fact that immunocompromised adults need PCV13 and two doses of PPSV23. They need to receive both vaccines, but there are different combinations of delivery and the intervals between those vaccines differ. In addition, if an adult has functional or anatomic asplenia, they need PCV13 and 2 doses of PPSV23, but certain other conditions like CSF leaks and cochlear implants require PCV13 and 1 dose PPSV23. Persons with chronic health conditions (e.g., heart disease, hypertension, kidney disease, and others) receive only 1 dose of PPSV23. People who smoke and residents of long-term care facilities receive 1 dose of PPSV23.

The addition of the recommendations for adults ≥ 65 years of age to receive PPSV23 contributed significantly to the complexity of incorporating the pneumococcal vaccination recommendations in the Adult Immunization Schedule. Also adding to the complexity is the need to account for adults 19 through 64 years of age who received pneumococcal vaccine(s) who then age into the ≥ 65 years of age category and may need PCV13 and PPSV23. Crafting easy-to-understand messages for busy healthcare providers is difficult. Figures must be interpreted with footnotes, so footnotes are of paramount importance and must contain the information needed by providers to implement ACIP recommendations.

Very few changes were made to the Pneumococcal Vaccination Recommendations in 2015. As noted earlier, the proposed changes for Figure 1 are to replace the purple bar with a yellow bar (recommended) for PCV13 for adults age ≥ 65 years. The lines are continuous rather than having broken yellow and purple lines. Vaccines for particular populations based on their medical and other conditions did not change. For the 2015 Adult Immunization Schedule, the footnotes basically revolve around adults 65 years of age and older by adding PCV13 on top of

PPSV23. The general recommendations include the following helpful information, with the last three bullets having already been included in previous versions of Adult Immunization Schedule Footnotes:

- When indicated, only one dose PCV13 is indicated for adults
- No additional dose of PPSV23 is needed if one was received at age ≥ 65 years
- Administer PCV13 before PPSV23 (but not at the same visit)
- Administer vaccines if vaccination history is unknown

As mentioned earlier, the pneumococcal vaccine intervals for adults became more complex with the addition of PCV13 needing to be administered for adults age ≥ 65 years. The interval between PCV13 and the subsequent PPSV23 should be 6 to 12 months in contrast to at least 8 weeks for the same schedule for person 19 through 64 years of age who are immunocompromised or who have asplenia, CSF leaks, or cochlear implants. The interval between the two PPSV23 doses is ≥ 5 years, which has not changed. Here are the footnotes reflecting the three age and risk groups in the 2015 footnotes:

Pneumococcal Vaccination Recommendations in 2015 Adult Immunization Schedule: Footnotes	
<ul style="list-style-type: none"> □ Adults ≥ 65 years <ul style="list-style-type: none"> • Have not received PCV13 or PPSV23, or unknown history • Have not received PCV13 but received PPSV23 at ≥ 65y • Have not received PCV13 but received ≥ 1 PPSV23 at 19–64y • Have received PCV13 but not PPSV23 at 19–64y • Have received PCV13 and ≥ 1 PPSV23 at 19–64y 	PCV13 → PPSV23 ¹ PCV13 ¹ PCV13 ¹ → PPSV23 ^{1,4} PPSV23 ^{1,4} PPSV23 ^{1,4}
<ul style="list-style-type: none"> □ Adults 19–64 years immunocompromised, asplenia <ul style="list-style-type: none"> • Have not received PCV13 or PPSV23, or unknown history • Have not received PCV13 but received 1 dose PPSV23 • Have not received PCV13 but received 2 doses PPSV23 • Have received PCV13 but not PPSV23 • Have received PCV13 and 1 dose PPSV23 	PCV13 → PPSV23 ¹ → PPSV23 ¹ PCV13 ¹ → PPSV23 ^{1,4} PCV13 ¹ PPSV23 ¹ → PPSV23 ^{1,4} PPSV23 ^{1,4}
<ul style="list-style-type: none"> □ Adults 19–64 years <ul style="list-style-type: none"> • CSF leaks, cochlear implants • Chronic health conditions • Smoke cigarettes or reside in long-term facilities 	PCV13 → PPSV23 ¹ PPSV23 PPSV23 <small>¹6–12 mos after PCV13</small> <small>²at least after PCV13</small> <small>³5y after most recent PPSV23</small> <small>⁴5y after most recent PPSV23</small>

This is basically an algorithmic approach. The footnote is designed for the busy provider to identify the patient by age and by health condition, and follow a menu to decide what the patient needs in terms of pneumococcal vaccine. The algorithm for adults age ≥ 65 years, immunocompromised persons 19 through 64 years of age, and adults age 19 through 64 years with chronic health conditions and other indications walks through what they may or may not have received during their pneumococcal immunization odyssey.

The next steps for the WG are to revise the 2015 Adult Immunization Schedule based on ACIP's discussion and recommendations, which will undergo another round of scrutiny by the influenza and pneumococcal influenza SMEs. Approval will be obtained from ACP, AAFP, ACOG, and ACNM. The revised schedule (figures, footnotes, and contraindications table) will then be submitted for CDC clearance. The goal is to submit the approved 2015 Adult Immunization Schedule to the *MMWR* and *Annals of Internal Medicine* in December for February 2015 publication. This will be done in coordination with the *MMWR* article on 2013 non-influenza vaccination coverage rates in the same week as adult immunization schedule release.

Discussion Points

Dr. Kinsinger (DVA) said she really liked the simplified algorithm, but would appreciate simplification of the interval between PCV13 and PPSV23 so that there is one interval regardless of age. She suggested considering whether the interval should be at least 8 weeks or 6 to 12 months. That would make programming electronic decision support tools much simpler. She also pointed out a gap in the schedule. For example, which schedule should be followed for a 65 year old patient who is pneumococcal vaccine naïve, who then becomes immunocompromised?

Dr. Kim responded that certain general information cases are included. When indicated, only one dose of PCV13 is needed and no additional PPSV23 is needed if one was received at age 65 years or older.

Dr. Kinsinger (DVA) suggested making it clearer that the guidance for immunocompromised persons who are 19 through 64 years of age does not apply to patients who are 65 years of age and older.

Dr. Temte reminded everyone that they could not change recommendations for pneumococcal pneumonia by virtue of changing the vaccination schedule. However, Dr. Bennett will take this back to the WG for consideration.

Dr. Bennett added that there was considerable discussion about this and no one was happy. There was a weighing between making the recommendations identical versus what will be the most possible recommendation to implement. The sense was that people who are immunocompromised see their physicians far more frequently than healthy people over 65 years of age. To state a greater than or equal to 8-week interval would imply that people have to receive it after 8 weeks. The concern was that more leeway is needed. The minimum recommendation is 8 weeks, but it can be extended. The WG is fully aware that this is not ideal and will discuss it again.

Dr. Belongia said he suspected that there was an inverse relationship between complexity and successful and implementation of guidelines such as this. Looking at each one makes sense, but looking at the whole picture makes it difficult to see how anyone could keep track of this. He wondered if it would be helpful to create two flow charts, one for immunocompromised persons and one for healthy persons or one for under and one for over 65 years of age. That way, the busy practitioner could go down the list to answer yes/no and get to the answer quickly versus reading all of the footnotes.

Dr. Kim replied that a write-up will be submitted for publication to the *MMWR* and the *Annals of Internal Medicine* in February 2015. In the *Annals of Internal Medicine*, there will be an opportunity to publish an algorithm that is more graphic in nature. A flow diagram will certainly be appropriate. This simply was not possible for the adult schedule, given the precious real estate on the footnotes.

Ms. Pellegrini pointed out that the fourth bullet on the list of contraindications for LAIV refers to children aged 2 to 4 years, which is not relevant for the adult schedule.

Referring to Slide 11, Dr. Temte reminded the WG to use the word “through” between age ranges. He also suggested rearranging the schedule to switch the category of Adults 19 through 64 years with Adults 19 through 64 years immunocompromised, asplenia.

Dr. Kempe reminded everyone that some nice piloting was done with providers for the childhood schedule, which found that providers thought the flowcharts were difficult to understand compared to patient-focused efforts. She suggested piloting the flowcharts with providers for the adult schedule as well.

Lynn Bozof (Minnesota Department of Health) noted that the footnotes refer to adults 65 years of age and older and PCV13 and PPSV23. While that is correct and everyone in the room understood what that meant, she thought they should be very specific about PCV13 first followed by PPSV23 6 to 12 months later. Even the schedule makes it look like both are to be given together, and many providers are likely to do that.

Ms. Groom (IHS) asked for clarification regarding whether the minimum interval to receive PPSV23 is 6 months for a 65 year old patient who received PCV13 before, meaning that if they received it at 8 weeks they would need a repeat dose. The absolute minimum interval should be spelled out in the pink table that shows the minimum age.

Dr. Bennett emphasized how difficult this has been and how impressed she was with how well Dr. Kim had condensed all of this complicated information into the chart.

On behalf of all of his colleagues in the Adult Immunization WG, Dr. Schaffner (NFID) extended his gratitude to Dr. Kim as well. He led the WG through this pneumococcal wilderness and always had good composure and a great sense of humor.

Regarding the contraindications and precautions table, Dr. Lett (CSTE) acknowledged that the language had been harmonized in terms of antivirals to correspond with the language in the influenza statement. However, there was now some discordance in the patient taking antivirals for the other live viral vaccines. Those were still in the precautions column and not the contraindications column. She wondered whether that could be further clarified following the vote, or if ACIP was voting on the language shown.

Dr. Carolyn Bridges (SME) said that the updated LAIV ACIP statement now says that in antiviral use, it is a contraindication. Antiviral use is a contraindication for LAIV, but is a precaution for varicella and zoster vaccines. The way it is in the table now is in concordance with published ACIP statement.

Dr. Lett (CSTE) said her sense was that this will cause confusion. There may be scientific reasons why they are not the same anymore, but people tend to keep that in mind more easily in terms of what is a precaution. If there is an opportunity, she suggested more discussion among the SMEs about harmonization for that.

Dr. Bridges (SME) said she was not clear whether this could be resolved without the other WGs being able to weigh in, particularly the Varicella and Zoster WGs.

Dr. Temte's reminded everyone that the adult schedule is intended to present existing policy rather than create new policy.

Dr. John Grabenstein (Merck) pointed out that there was some inconsistency in the footnote information shown in Slide 11 in that some of the wording states “have not received X but have received Y” and some are written “have received X but not Y.” Clinicians tend to think of what someone has received and that tells them what is missing, so he suggested standardizing those.

Dr. Schuchat thought that the footnote made sense for Adults ≥ 65 years in terms of the use of “have not received” and “have received” and suggested not changing it.

Ms. Pellegrini agreed with Dr. Schuchat because PCV is a single dose versus PPSV sometimes being two doses. It is easier to think about PCV in a binary way as a first screen to determine whether someone has received one or two doses of PPSV.

It was noted that the language should read “6 to 12 months” and not “6 through 12 months” because people might think after a year they should no longer give this vaccine.

Vote: 2015 Adult Immunization Schedule

Dr. Bennett made a motion to approve the Adult Immunization Schedule as proposed. Dr. Riley seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. Two members were absent. The disposition of the vote was as follows:

13 Favored: Bennett, Belongia, Bocchini, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A
2 Absent: Campos-Outcalt, Harriman

Public Comment

Dr. Sandra Fryhofer ACP Liaison

Dr. Fryhofer thanked ACIP for voting on this new adult schedule on behalf of the ACP, the nation’s largest medical specialty society, representing over 141,000 doctors of internal medicine, medical students, residents, and fellows, as well as on behalf of patients. She also offered special thanks to the WG for putting together the new pneumococcal mega-footnote. She said that she preferred the new title “ACIP’s Pneumococcal Odyssey,” with the goal being to help practitioners more easily implement this new schedule. Pneumococcal infection is a major cause of morbidity and mortality and has killed as many as 4000 people in the US each year, primarily adults. Older adults are at increased risk for invasive disease, and doctors of internal medicine provide regular care to the majority of patients affected by these new recommendations.

ACIP has done its work and now it is in ACP’s hands. ACP will work to get the word out about the new schedule, and has an adult immunization committee that meets regularly and is open to new ideas and new partnering. Current plans include a dedicated immunization portal where all immunization materials and programs will be updated. This includes ACP’s adult immunization app and adult immunization guide. ACP also has several ongoing quality improvement (QI)

immunization initiatives, including a CDC-funded QI program and a new “I Raise the Rates” program. ACP also plans to have a coaching call on pneumococcal vaccination for these programs. As noted, the new schedule will be published in February 2015 in the *Annals of Internal Medicine*. The most recent impact factor for this publication is 16.104, which is the highest of any specialty journal in the Thomson Reuters’ General and Internal Medicine category. This new recommendation is both comprehensive and complicated, but patients will benefit from collective immunization implementation efforts.

Hepatitis Vaccines

Introduction

Art Reingold, MD ACIP Hepatitis Work Group Chair

Dr. Reingold reminded everyone that the Hepatitis Vaccine WG was tasked with updating the recommendations for hepatitis A and B vaccines, and the decision was made to begin with hepatitis A. There are existing hepatitis A and B vaccine recommendations. The current recommendations and updates for hepatitis A vaccine include the following:

- ❑ ACIP Routine Recommendation for Hepatitis A Vaccine (2006). *MMWR* 2006 May 19;55(RR-7):1-23.
- ❑ Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the ACIP. *MMWR* 2007 Oct 19;56(41):1080-4.
- ❑ Updated recommendations from the ACIP for use of hepatitis A vaccine in close contacts of newly arriving international adoptees. *MMWR* 2009 Sep 18;58(36):1006-7.
- ❑ FDA Approval of an Alternate Dosing Schedule for Twinrix®. *MMWR* 2007 Oct 12;56(40):1057.

Since the June 2014 ACIP meeting, the WG has had five teleconferences focused on hepatitis A vaccine coverage, the epidemiology of hepatitis A in the US, the hepatitis A multi-state outbreak and foodborne disease, and hepatitis A hospitalization trends. The presentation during this session focused largely on hepatitis A burden of disease and the population that still may require protection.

In the short-term, the WG will continue to discuss updating the hepatitis A vaccination statement from 2006 and catch-up vaccination for children/teens age 2 through 18 years of age. The WG will continue to evaluate evidence, including GRADE and cost-effectiveness as data are available. Long-term plans are for the WG to discuss hepatitis A vaccine for PEP in adults 40 years of age and older. While the burden of disease for hepatitis A is certainly much lower than it used to be, there are still gaps in immunity, particularly with the increase in importation of foods that pose a risk of hepatitis A infection.

Update on Hepatitis A Burden and Hepatitis A Population Protection

Noele Nelson, MD, PhD, MPH

Vaccine Research and Policy Unit

Division of Viral Hepatitis

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

During this session, Dr. Nelson discussed hepatitis A vaccine history in the US, epidemiology of the disease, vaccine coverage, antibody to hepatitis A virus (anti-HAV), seroprevalence, and the hepatitis A outbreak and food-associated exposure risk. Hepatitis A vaccination was introduced incrementally in the US from 1996 to 1999. In 1996, vaccine was recommended for children at age 2 years in communities with high rates of disease and children through teen years in outbreaks. In 1999, vaccine was recommended for children at age 2 years of age in 11 states (Washington, Oregon, Idaho, California, Nevada, Utah, Arizona, NM, OK, SD, Alaska) with average annual hepatitis A rates of two times the national average at ≥ 20 cases per 100,000 population. Vaccine was considered in 6 states (Missouri, Montana, Wyoming, Colorado, Texas, Arkansas) with rates above the national average at ≥ 10 cases per 100,000 population [MMWR 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)].

Universal childhood vaccination was introduced in 2006. Vaccine was recommended for use at age 12 through 23 months in all states. It was recommended that existing vaccination programs for ages 2 through 18 years should be considered, and catch-up vaccination should be continued in outbreaks and areas with increasing disease rates. Vaccine was also recommended for any person wishing to obtain immunity. There is no routine vaccine recommendation for children over 23 months of age. In addition, vaccine is recommended for groups at increased risk of HAV infection or severe disease, such as the following:

- Travelers
- Men who have sex with men (MSM)
- Users of injection and non-injection drugs
- Persons with clotting-factor disorders
- Persons who work with nonhuman primates
- Persons who anticipate close personal contact with an international adoptee
- Persons with chronic liver disease
- PEP for healthy persons 12 months through 40 years of age

Regarding hepatitis A epidemiology, data collection for hepatitis A started in 1966. The highest number of hepatitis A cases reported was in 1971 at approximately 60,000 cases at a rate of about 30 cases per 100,000 population. Vaccine was recommended in 1996. The number of reported cases declined from 31,032 in 1996 to 1,398 cases in 2011. The rate also declined from 11.7 cases per 100,000 population in 1996 to 0.4 cases per 100,000 population in 2011. From 1996 to 2011, there was a 95.5% decrease in reported cases [National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. *Pediatrics* 2007;119:e22-9].

In 2011, the number of reported cases in the US reached an all-time low of 1,398 cases. In 2012, the number of reported cases in the US increased to 1,562 cases, representing the first increase in cases since 1995. In 2013, the number of reported cases in the US increased again to 1,781 cases. Though these increases are not large at this point, and most of the increase in 2013 is attributable to a multi-state hepatitis A outbreak, the increases from 2011 to 2013 represent a reversal of a trend over almost two decades. CDC is exploring the etiologies of the

case increases, including reporting biases, and the geographic distribution of the cases [National Notifiable Diseases Surveillance System (NNDSS); DVH Surveillance report (2008-2012); Noninfluenza vaccination coverage among adults - United States, 2012. *MMWR*. 2014 Feb 7;63(5):95-102].

Increases in the rate of cases from 2011 to 2012 were reported in 4 regions. Increases in the rate of cases from 2012 to 2013 were reported in 6 regions, although there was a decrease in one region. The multi-state outbreak in 2013 was reported primarily in the Mountain and Pacific Regions among 8 states. However, increases from 2012 to 2013 were observed in other regions as well. When looking at these data at the state level, it was observed that some of the increases in rates occurred in states not involved in the outbreak, suggesting multiple causes for the increase in number and rate of cases [National Notifiable Diseases Surveillance System (NNDSS); DVH Surveillance report (2008-2012); Noninfluenza vaccination coverage among adults - United States, 2012. *MMWR*. 2014 Feb 7;63(5):95-102].

Rates of acute hepatitis A declined for all age groups from 2000 to 2012. Rates were similar and low among persons in all age groups in 2012 with less than 1.0 case per 100,000 population. In 2012, rates were highest for persons aged 20 through 29 years at 0.69 cases per 100,000 population. The lowest rates were among children less than 9 years of age at 0.15 cases per 100,000 population. Starting in 2007, children less than 9 years of age had the lowest rate of infection in any age group. The Healthy People 2020 target is 0.3 cases per 100,000 population. Only the 0 through 9 years age group has declined to a rate lower than 0.3 per 100,000. Of note, the rates increased from 2011 to 2012 for ages 20 through 29 years and ages 40 and above [National Notifiable Diseases Surveillance System (NNDSS); <http://www.healthypeople.gov/2020/topicsobjectives2020/pdfs/immunization.pdf>].

Looking at the data separately by decade of life for children (0-9 years, 10-19 years) and all adults (age 20 years and older) from 2008 to 2012, it is clear that the largest percentage of hepatitis A cases are occurring in adults [National Notifiable Diseases Surveillance System (NNDSS); DVH Surveillance report (2008-2012); Noninfluenza vaccination coverage among adults - United States, 2012. *MMWR*. 2014 Feb 7;63(5):95-102].

Taking a further look at burden of disease, a recent paper by Collier et. al. analyzed Hepatitis A hospitalization trends from 2002 to 2011, using primary discharge diagnosis data (ICD9 codes) from the National Inpatient Sample Healthcare Utilization Project (HCUP). Though a decrease in hepatitis A hospitalization rates was observed overall from 0.72 per 100,000 in 2002 to 2003 to 0.29 per 100,000 in 2010 to 2011, the mean age of persons hospitalized for hepatitis A has increased significantly over the study time period from a mean age of 37.6 years in 2002 to 2003 compared to 45.5 years in 2010 to 2011 [Collier MG, Tong X, Xu F. Hepatitis A hospitalizations in the United States, 2002 - 2011. *Hepatology*. 2014 Sep 29].

Based on information from case surveillance in National Notifiable Diseases Surveillance System (NNDSS) data regarding hospitalizations in reported hepatitis A cases, many cases are reported without hospitalization information. From 2009 to 2012, 35% to 45% of cases do not have data on hospitalization. Therefore, the number of cases hospitalized is likely underestimated. Of HAV cases, 39.3% were hospitalized in 2009 and 45.8% in 2012. Since 2009, hospitalizations have been increasing. Though hepatitis A hospitalization rates have decreased overall, as shown by National Inpatient Sample primary diagnosis code data, surveillance data shows that hospitalization rates for all reported hepatitis A cases increased from 39% of cases in 2009 to 46% of cases in 2012. Looking further back, this trend of

increasing hospitalization rates for reported cases has been observed since 2005 with lower rates of 33% in 2005 [National Notifiable Diseases Surveillance System (NNDSS); Division of Viral Hepatitis Surveillance Report (2009-2012)].

Deaths have declined since vaccine introduction for all age groups. The number of deaths approaches 0 for age groups less than 50 years. The total number of deaths in 2012 was 23. Of those, 21 deaths were in the 50+ age group and 2 deaths were in the 20 through 49 age group. These numbers increase slightly when multiple causes of death are considered [NCHS mortality files for vaccine preventable diseases (1990-2012)].

Regarding who is getting infected with hepatitis A virus, patients were asked about engagement in selected risk behaviors and exposures during the incubation period, 2 to 6 weeks prior to onset of symptoms. Data were collected as part of CDC's NNDSS via passive surveillance through voluntary reporting from state health departments. Of the 1,562 case reports of acute hepatitis A received by CDC during 2012, a total of 568 (36%) cases did not include a response (i.e., a "yes" or "no" response to any of the questions about risk behaviors and exposures) making assessment of risk behaviors or exposures challenging. Of the 994 case reports that had a response, 80% (n=793) indicated no risk behaviors/exposures for acute hepatitis A, while 20% (n=201) indicated at least one risk behavior/exposure for acute hepatitis A during the 2 to 6 weeks prior to onset of illness. Travel was the most identified risk factor. Of the 713 case reports that had information about travel, about 13% (n= 92) involved persons who had traveled outside the US or Canada. Foodborne or waterborne exposures were reported less frequently; however, foodborne exposure is a growing area of concern and may represent a percentage of the cases with no risk factor identified [National Notifiable Diseases Surveillance System (NNDSS)].

Because risk factor information is often missing (i.e., no response to risk factor questions), and to collect supplemental information, select health departments are funded to conduct enhanced, population-based surveillance. An analysis of these data from 2005 through 2007 occurred at 6 Emerging Infection Program (EIP) sites, covering an estimated 30 million population. For risk factors reported by cases in the EIP sites during 2005 to 2007, there are less missing data in funded sites compared to the NNDSS data. However, the distribution of risk factors was comparable. Travel was the most frequently reported risk factor (47% of cases with a positive response), including persons with direct international travel, and those who had contact with someone who traveled. This is much higher than the approximately 13% reported by passive surveillance, and much higher than observed in the 1980s and 1990s (4%). The molecular characteristics of a sample of cases confirmed they were travel related. The strains were related to Mexican and some Brazilian hepatitis A viral strains. Though these data are from 2005 to 2007, it is believed that the data are similar today. Of note, over 35% of cases reported an unknown risk factor. Foodborne exposure may represent a percentage of these unknown exposures. However, based on risk data collected by both the NNDSS and the EIP Hepatitis Surveillance Sites, no significant association between risk factor and the increase in hepatitis A cases from 2011 to 2013 can be made at this time [Klevens et al. The Evolving Epidemiology of Hepatitis A in the United States. *Arch Intern Med.* 2010 Nov 8;170(20):1811-8].

The wider use of vaccine is largely responsible for the marked decrease in hepatitis A morbidity; however, vaccination rates remain low. Hepatitis A vaccine is recommended in a 2-dose series. In 2012, Hepatitis A vaccine coverage for children 19 through 35 months of age was 81.5% and 53% for ≥ 1 and ≥ 2 doses, respectively. This is substantially less than the Healthy People 2020 target of 85% for two dose coverage level in this age group [Elam-Evans LD, et. al. National,

state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2013. *MMWR*. 2014 Aug 29;63(34):741-8].

In 2012, coverage among adolescents 13 through 17 years old was estimated to be about 60% and about 48% for ≥ 1 and ≥ 2 doses, respectively based on preliminary data. Only ≥ 3 dose HPV vaccine coverage has lower teen vaccine coverage than 2-dose hepatitis A vaccine. Of the adolescent vaccines routinely recommended, there is no hepatitis A recommendation for children over 23 months of age, while HPV (2007), Tdap (2006), and Meningococcal (2006) are routinely recommended for adolescents [Elam-Evans LD, et. al. National, state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2013. *MMWR*. 2014 Aug 29;63(34):741-8].

Two-dose coverage for adults ages 19 through 49 years is 12.5% overall. The vaccine coverage for persons with chronic liver disease, a high risk group, is 17%. Vaccine coverage is 20% for travelers. Therefore, the age groups with the highest death rate have the lowest vaccination coverage. The data source is the National Health Interview Survey (NHIS), which collects information about the health and health care of the non-institutionalized civilian population in the United States using nationally representative samples [Noninfluenza vaccination coverage among adults - United States, 2011. *MMWR*. 2013 Feb 1;62(4):66].

According to National Health and Nutrition Examination Survey (NHANES) data, significant increases occurred in the proportion of children with protection for ages 6 through 11 years and 12 through 19 years, most likely due to vaccination. Minimal change in prevalence occurred among adults 20 through 29 and 30 through 39 years of age. However, significant decreases occurred in the proportion of adults with protection for ages 40 through 60 years and older. Overall, the prevalence of antibody among US residents remained about the same between the two surveys, 39% and 35%, respectively, indicating that only 1/3 of the US population had protection against hepatitis A infection in 2009 to 2010. The lowest prevalence of antibody was among adults [NHANES, National Health and Nutrition Examination Survey (ALL US ADULTS)].

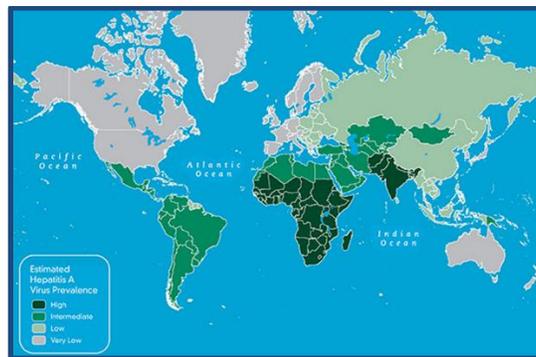
A multistate hepatitis A outbreak occurred in the US in May 2013. The outbreak was associated with contaminated pomegranate arils imported from Turkey and illustrates ongoing hepatitis A exposures and adult susceptibility. There were 165 cases in 10 states. Most (93%) cases in the outbreak were aged ≥ 18 years. Overall, 44% of all cases were hospitalized and 45% of adult cases were hospitalized. Two cases developed fulminant hepatitis, and one required a liver transplant. In addition, multiple recent berry-associated outbreaks in Europe have been reported. Of note, the percent reported hospitalized in the outbreak (44%) is very consistent with the percent of hepatitis A cases hospitalized in 2011 based on case surveillance data (43%) [Collier MG, et. al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. *Lancet Infect Dis*. 2014 Oct;14(10):976-81].

Based on surveillance data, travel is the most reported risk factor for hepatitis A. However, there is a growing concern about the risk of exposure from contaminated food. The volume of imported fruit and vegetables in the US has increased from 1999 to 2013. Last year, the US imported over 12 million tons of fruit, and almost 9 million tons of vegetables. Imported fruit and vegetables originate from countries where hepatitis A is endemic, which are shown in the following table:

Fruit	Vegetables
Mexico	Mexico
Chile	Peru
Costa Rica	Guatemala
Guatemala	India
Ecuador	
Argentina	
Brazil	

Note that Turkey is not one of the countries listed [<http://www.ers.usda.gov/data-products/us-food-imports.aspx>].

The following map shows the estimated prevalence of hepatitis A virus in 2005, with the moderate and dark green representing areas of intermediate and high hepatitis A viral prevalence:



In summary, an increasing proportion of adults in the US are susceptible to hepatitis A. This is due to reduced exposure to HAV early in life, significant decreases in anti-HAV seroprevalence in adults 40 years of age and older, and low 2-dose vaccination coverage in adults. This is important because it is known that morbidity and mortality increases with age. Suboptimal 1- and 2-dose vaccination coverage also exists among children. An increase in HAV cases was observed from 2011 to 2012 and from 2012 to 2013. These represent the first increases since 1995 to 1996. HAV infection rates also increased from 2011 to 2012 for ages 20 through 29 years and ages 40 years and above. The mean age of persons hospitalized for hepatitis A increased significantly from 2002 to 2003 to 2010 to 2011. Hospitalization rates for reported hepatitis A cases increased from 2005 to 2011. HAV remains endemic in many areas of the world. Risk exists for travelers to intermediate and high endemic countries, as well as for consumption of imported HAV contaminated food from global sources. Herd protection does not prevent foodborne exposure. No routine or catch-up hepatitis A vaccine recommendation exists for adolescents or adults.

The ACIP Hepatitis WG is currently focusing on updating the 2006 hepatitis A vaccination statement and discussing strategies to address the increasing number/rate of acute hepatitis A cases and continue progress toward the healthy people 2020 goal of 0.3 cases per 100,000 population. The WG is discussing catch-up vaccination for children and teens 2 through 18 years of age. Justification for expanding the age range of childhood vaccination to age 18 includes: 1) continuing exposure to hepatitis A virus; 2) future protection of the adult population, since an increasing proportion of US adults are susceptible to HAV infection, and 3) maximizing herd protection from childhood vaccination. The WG is also discussing other strategies such as

vaccination for other ages. Additional information and evaluation of the evidence is needed before WG consensus can be reached.

Additional information that would be helpful in support of expanding the age range for universal hepatitis A vaccination includes: 1) modelling hepatitis A disease and cost-effectiveness with higher hepatitis A vaccination coverage among children and adolescents and/or subsets of adults, for which planning is underway; and 2) GRADE for hepatitis A one- and two-dose vaccine efficacy, safety, and long-term protection, for which a systematic review is in progress. In addition, as became evident during the multi-state outbreak, more data are needed on vaccine efficacy for PEP in adults 40 years of age and older, for which planning is underway.

Discussion Points

Dr. Karron said she suspects that given the intervals between the first and second dose, many travelers go to travel clinics for the first dose shortly before traveling, but never return for the second. Given this dismal data, she asked whether Dr. Nelson had coverage information for one dose in travelers. Her understanding was that two doses are given to sustain immunity, but very often protective levels of antibody are achieved following a single dose.

Dr. Nelson responded that she did not have data based on one dose. A study of delayed booster doses in those over two months of age showed that boosters delayed up to 31 months have comparable results. Argentina has a one-dose universal hepatitis A vaccine strategy for children with about five years of follow-up data available. For two-doses, studies modeling long-term protection suggest vaccine protection for at least 25 years or more.

Dr. Reingold agreed, noting that when he was on SAGE, countries were given permission to use a one-dose schedule based on the Argentina data. The data are quite convincing that one dose is highly efficacious, but the duration of protection is somewhat uncertain.

Dr. Kempe noted that on the schedule, hepatitis A vaccine is recommended for catch-up after two years of age through adolescence. She agrees that education and focused encouragement are important, but that seems to be part of the current schedule.

Dr. Nelson replied that the schedule is for 12 through 23 months, and the recommendation indicates that catch-up can be considered.

Dr. Pickering stressed that catch-up is not recommended routinely for those two years of age and older. That way of handling things does not seem to be working, because children are not being immunized. A very low percentage of adults who develop hepatitis B or C are immunized against hepatitis A. He expressed his hope that the WG is discussing a stronger consideration than "should be encouraged," which is the wording on the schedule.

Dr. Bennett asked whether it would be possible to look at the data from the EIP for potential sources of infections or risk factors by age to identify the potentially greatest strategies for decreasing risk.

Dr. Schaffner (NFID) added that he was particularly interested in the age and sex distribution of the "unknowns."

Dr. Nelson replied that while she did not have those data to present at this time, they are important to understand. CDC is trying to further define the “unknown” group, which is quite large.

Dr. Gorman (NIH) asked whether there is a difference between the rate of spontaneous and augmented hepatitis reported among the centers. His concern was that as the disease becomes rarer, people are more likely to report it because it is unusual. From an unscientific survey of his three adult children between the ages of 20 and 29, all three have traveled to high risk countries. That may be a much more common event in the generation between 1995 and 2012 than in prior generations. The increase may be that they are exposing themselves to more risk factors rather than some other vaccination-related episode.

Dr. Nelson replied that she was not aware of a difference between the rate of spontaneous and augmented hepatitis reported.

Dr. Temte asked what is known about patients with more severe disease and hospitalization and how many of them have chronic liver disease as a risk factor, given that we do an atrocious job of immunizing patients with chronic hepatitis C and alcoholics with chronic liver disease.

Dr. Nelson responded that she did not know how many severe cases have chronic liver disease; however, CDC has analyzed data on liver failure and liver transplant hepatitis A virus cases and did not observe a trend over time.

Ms. Pellegrini emphasized that another barrier for travelers who may be at risk is that travel vaccines tend not to be covered by health insurance.

Day 1: Public Comment

No public comments were offered during this session.

Meningococcal Vaccines

Announcement

Dr. Wellington Sun
ACIP Liaison
Food and Drug Administration

During the Unfinished Business session, Dr. Sun announced the approval of Pfizer’s meningitis B vaccine on October 29, 2014. It was included with the information for the Meningococcal Vaccines session for continuity and ease of reading.

Dr. Sun reported that the meningitis B vaccine developed by Pfizer is based on surface proteins, so in this regard it differs from all previous *Neisseria meningitidis* vaccines that are based on the capsular polysaccharide. The indication for this vaccine is for prevention of invasive disease caused by serogroup B *Neisseria meningitidis* in persons 10 through 25 years of age. This

serogroup has caused several outbreaks on college campuses and represents a public health need. The FDA granted a breakthrough therapy designation on this vaccine with that in mind. This allowed the agency to focus its resources, along with the manufacturer, to make the development pathway more efficient and allow the FDA to perform what is known as a “rolling review” of the licensing application, which greatly sped up the process. The approval was ultimately based on a determination of safety and effectiveness. Effectiveness was demonstrated by serum bactericidal antibody levels against four representative strains of *Neisseria meningitidis* in studies of about 2800 subjects. The safety database included over 4000 subjects in the US, Europe, and Australia. Because the approval is based on the serum bactericidal antibody levels, Pfizer is required to conduct further studies after licensure to show breadth of coverage against other strains. FDA looks forward to ACIP’s discussion guiding the use of this vaccine.

Introduction

Lorry Rubin, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

Dr. Rubin introduced the meningococcal vaccine session. As reported by Dr. Sun, rLP2086 (Trumenba[®]) by Pfizer was licensed in the US for persons 10 through 25 years of age on October 29, 2014. 4CMenB (Bexsero[®]) by Novartis is currently under FDA review for persons 10 through 25 years of age. These meningococcal B vaccines are distinct from the conjugate MenACWY vaccines because they are based on immunity to proteins rather than capsular polysaccharides.

Meningococcal B vaccine has been used for outbreak responses. In 2013, two universities experienced outbreaks of serogroup B meningococcal disease with a combined 13 cases and one death reported. Vaccination campaigns were conducted at both universities in response to the outbreaks using one of the investigational MenB vaccines made by Novartis, which was obtained through an expanded access Investigational New Drug (IND) application sponsored by CDC. Guidance for use of serogroup B vaccines in institutional outbreaks has been developed and is available at: <http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf>

Presentations were given during this session on 4CMenB (Bexsero[®]) by Novartis, rLP2086 (Trumenba[®]) by Pfizer, the epidemiology of serogroup B meningococcal disease in the US, and an overview of serogroup B meningococcal vaccines and considerations for use. In terms of the timeline, proposed recommendations will be presented during the February 2015 ACIP meeting for use of serogroup B vaccines in persons ≥ 10 years of age with high-risk medical conditions, laboratory workers, and outbreaks. The ACIP Meningococcal Vaccines WG will review data on MenB vaccines as it becomes available and will continue discussions on use and potential impact of these vaccines. Updated outbreak control guidelines will be developed which address outbreaks due to all serogroups.

4CMenB Serogroup B Meningococcal Vaccine

James Wassil MSc MBA
Clinical Development
Novartis Vaccines

Mr. Wassil discussed the BLA accepted by the FDA's Center for Biologics Evaluation and Research (CBER); 4CMenB candidate vaccine characteristics (e.g., proposed indication, vaccine composition, and estimated strain coverage); and clinical data in adolescents and young adults (e.g., pivotal trial data, supplemental data in persons from the US, and the demonstrated safety profile).

Based on the proposed indications currently under review with the FDA, 4CMenB will be indicated for prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. 4CMenB is a sterile suspension for intramuscular injection that is to be administered as 2 doses, each 0.5 mL, with an interval of at least 1 month between doses. It is fully liquid so it does not require reconstitution, but it does require refrigeration at 36°F to 46°F (2°C to 8°C), cannot be frozen, and needs to be protected from light.

The serogroup B capsule is very poorly immunogenic. As a consequence, vaccine development strategies have focused on subcapsular protein antigens, but these are highly diverse. To address the diversity, Novartis took two approaches. The first was targeted to conserved antigens through a process called reverse vaccinology. The second was that it developed a multi-component approach; that is, by adding multiple subcapsular proteins into the vaccine. The goal was to achieve broad coverage against the circulating serogroup B strains. The vaccine is formulated with 50 µg each of three recombinant proteins: factor H binding protein (fHbp), Neisserial adhesin A (NadA), and a Neisseria heparin binding antigen (NHBA). The fourth component is 25 µg of outer membrane vesicles (OMV). This is the same OMV that was used in New Zealand to address a clonal outbreak, so safety and effectiveness has been demonstrated with over 3 million doses administered in that campaign. All four of these components are then adsorbed onto Aluminum (Al³⁺).

Regarding predicted strain coverage for 4CMenB, coverage is assessed based on an enzyme-linked immunosorbent assay (ELISA) called the Meningococcal Antigen Typing System (MATS). The MATS ELISA is correlated with killing of strains by vaccine-induced antibodies in the serum antibacterial assay. A serum bactericidal activity (SBA) with a titer $\geq 1:4$ is considered the correlate of protection against this disease. In MATS, if a strain exceeds a minimum threshold value for any one of the recombinant protein ELISAs or its genotype is PorA 1.4, it is highly likely that this strain would be killed in SBA and is, therefore, considered to be covered.

In the US, coverage is assessed based upon a representative panel of 442 strains isolated from individuals between 2000 and 2008. Based on MATS, only 9% of strains were not covered from the strain panel. Of the 91 that were covered, 44% were covered by one vaccine component. However, over half of covered strains were covered by two or more components in the vaccine. That is, independently, each component was deemed sufficient to kill the strain on its own. For the subset of strains where the disease occurred in individuals 10 through 25 years of age, the predicted coverage did not change substantially at 92%. It is worth noting that the number of strains that are covered by multiple antigens did increase up to 61%.

In the 4CMenB trials conducted in adolescents and adults, 18,400 subjects received at least one dose of 4CMenB. In addition, over 6,000 individuals between 2 months and 10 years of age also received the vaccine. That contributes to the overall clinical database for this product. Focusing on the clinical studies that are supportive of the indication being sought in the US, 3,139 subjects 10 through 50 years of age received at least one dose of the vaccine in six randomized control clinical studies. In addition, over 15,000 subjects received at least one dose at Princeton University or the University of California Santa Barbara under a CDC-sponsored expanded-use IND. Those results were presented to ACIP during previous meetings. For this session, Mr. Wassil focused on two studies: 1) V72P10/E1, a Phase IIb/III study conducted in Chile in healthy adolescents 11 through 17 years of age to assess different dosing schedules and persistence of antibodies; and 2) V102_03, a Phase II study conducted in the US and Poland among healthy adolescents and young adults 10 through 25 years of age to assess the safety and immunogenicity of an investigational ABCWY vaccine. It is important to note that this study included one arm in which individuals 10 through 25 years of age in the US received 4CMenB as a comparator.

In summary, the 4CMenB clinical data in adolescents and adults showed that the vaccine is immunogenic after two doses in a variety of schedules. This has also been confirmed in a small US study. Persistence of protective titers has been demonstrated for up to 23 months after the 2-dose schedule. The demonstrated safety profile includes three recently conducted large-scale vaccine campaigns (Princeton and Santa Barbara). A third was conducted in Saguenay-Lac-Saint-John region of Quebec in over 43,000 individuals 2 months through 20 years of age who received at least one dose of the vaccine. The Ministry of Health of Quebec conducted active safety surveillance, with over 12,000 subjects keeping diary cards for seven days after vaccination. Overall, the safety profile observed in these campaigns were consistent with that observed in clinical studies.

The V72P10 study evaluated the safety and immunogenicity of 1-, 2-, and 3-dose schedules in 1,625 subjects. Blood was drawn after each visit, and safety was followed up for 12 months. The primary endpoint of this clinical study was the percent of subjects with human serum bactericidal assay (hSBA) titers $\geq 1:4$. Immunogenicity was measured for each vaccine component by use of indicator strains, which were uniquely susceptible to killing in SBA to only one component of the vaccine. In the interest of time, Mr. Wassil did not show the results from the 3-dose arm because there was no statistically significant difference between hSBA GMTs titers for those who received 2 doses and those who received 3 doses. The vaccine demonstrated robust immune responses in this age group with several 2-dose schedules. One month after the second dose, 99% to 100% of subjects achieved hSBA titers $\geq 1:4$. There was no difference in the seroresponse rate across dosing schedules.

It is important to note that an indicator strain was not identified for NHBA at the start of the study, so the analysis was done post hoc. Because of this, not all of the analyses were conducted. Also for NHBA in this study, there were high pre-titers to the strain, presumably due to previous nasopharyngeal carriage. Robust responses were indicative for each of the four vaccine components and for all three 2-dose schedules. Tolerability was assessed in this study by comparing against an aluminum-based placebo and stratifying by severity. In general, the most common local reactions included pain at injection site and erythema. The most common systemic reactions were malaise, myalgia, and headache. Both were the most common in both the vaccine group and placebo group, respectively. Reactogenicity was higher in recipients of the vaccine compared to the placebo, but the majority of these were reported as mild to moderate and transient. Fever was uncommon and relatively similar in both groups, and fever

above 39 degrees Celcius was rare. There was no evidence of increasing severity with subsequent doses, and tolerability was acceptable to study participants as evidenced by the fact that there were low rates of study withdrawals.

Persistence of antibodies was measured between 18 and 23 months after completion of the 2-dose series (18 months after 0-6 schedule, 22 months after 0-2 schedule, 23 months after 0-1 schedule). Overall, the majority of subjects retained seroprotective levels, with 75% to 95% maintaining titers above 1:4. The dosing schedule did not appear to have an impact on the persistence of the seroprotective rates. In terms of antibody persistence based on hSBA GMTs 18 to 23 months after the completion of the 2-dose series, GMTs overall did wane as would be expected. However, they still remained higher than their corresponding pre-vaccination titers.

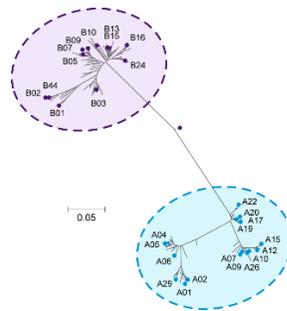
As noted earlier, Study V102_03 assessed different formulations of ABCWY vaccine in US and Polish subjects 10 through 25 years of age. This study included one arm in which 4CMenB was used as a comparator, given on a 0- and 2-month schedule. In terms of the percent of subjects with titers $\geq 1:5$ for each of the corresponding fHbp, NadA, PorA, and NhbA antigens at baseline and one month after a 2-dose series, baseline titers compared to Chile were much lower. However, robust responses were achieved with 73% to 90% of adolescents achieving titers above 1:5.

In summary, the BLA for 4CMenB has been accepted by the FDA and priority review status has been granted. Based upon the studies, 4CMenB is believed to generate a protective immune response in adolescents after two doses. This was confirmed in a small US study. Persistence of antibodies was demonstrated up to two years after the last dose. There was no statistically significant difference in hSBA GMTs between subjects receiving two doses or three doses of vaccines when assessing the indicator strains. Novartis has begun to collect real-life experience with this vaccine, which has been approved in 35 countries. Over a million doses have been distributed. Based on the safety data generated from over 30,000 doses at Princeton and the University of California Santa Barbara and over 55,000 doses in Saguenay-Lac-Saint-John, no particular concern for any specific event was identified in either campaign.

rLP2086 Serogroup B Meningococcal Vaccine

Dr. Laura York
Global Meningococcal Lead
Medical Development, Scientific and Clinical Affairs
Pfizer

On behalf of the many people who worked long and hard along with the FDA to license Trumenba[®] meningococcal group B vaccine, Dr. York expressed Pfizer's excitement about the FDA approval received the previous day. This vaccine was introduced to ACIP as rLP2086, and Pfizer often refers to it as bivalent rLP2086. Bivalent rLP2086, Pfizer's meningococcal group B vaccine, is based on the lipoprotein 2086. This is a surface-exposed fHbp expressed in over 97% of invasive meningococcal B strains. It is a conserved protein, and the gene is rarely absent from meningococcal B. The fHbp sequences segregate into two genetically and immunologically distinct subfamilies, A and B as shown in the phylogenetic tree:

Subfamily B: 71%**Subfamily A: 29%**

The length of the line identifies the similarity between those variants. The variants within a subfamily are highly related and have over 84% sequence identity. The bivalent vaccine contains two lipidated fHbp variants (A05 and B01), one from each subfamily to give complete protection across the two subfamilies.

The vaccine design of a bivalent lipidated protein was supported by preclinical data. Consideration was given to monovalent vaccines and bivalent vaccines composed of the subfamilies A and B. Rabbits were immunized with the monovalent or bivalent vaccine. The ability of the immune sera to kill diverse MenB strains in an hSBA was assessed. The strains would express either as subfamily A or subfamily B, and the ability to kill in terms of an SBA that included rabbit complement. If a rabbit was inoculated with the monovalent vaccine of A05, there were good responses across the variation in the A subfamily, but not so much across the strains that express the B variants. Similarly, this predominantly subfamily-specific type of response was observed in animals inoculated with a B01 monovalent (e.g., good responses across the strains that express subfamily B variants, but not across the A). Only a vaccine that contains a protein from both of these subfamilies provides protection across the strains that express either A or B subfamilies.

These data supported Pfizer in moving into clinical trials. Pfizer submitted an IND to the FDA in April 2008, and FDA-Pfizer collaborative discussions were initiated to define the licensure pathway for MenB vaccines in the US. A significant step was the decision that the SBA incorporating human complement could be used as the correlate to predict protection. In June 2012, FDA and Pfizer reached agreement on immunogenicity endpoints based on measurement of hSBA responses. All ongoing studies were modified to provide prospective, blinded data based on the agreed upon endpoints. The length of time it took to come to those agreements reflects the complexity of defining the endpoints that would evaluate and demonstrate that a vaccine would be able to protect broadly across the variation seen in this protein.

FDA licensure will be based on sufficient numbers of US subjects to show safety and hSBA responses (correlate to predict protection). In a clinical trial, there are limitations in the amount of serum. To be able to test, there must be validated assays with strains. The number of strains that can be tested are limited. However, in Phase I and II clinical studies, Pfizer had hSBA data that clearly supported and confirmed the information that was developed in the preclinical studies that the immune sera following three doses demonstrated activity against strains bearing different variants. The FDA and Pfizer came to an agreement that the hSBA responses against four MenB test strains one month post-dose 3 was the endpoint for four strains. Four strains were selected in an unbiased fashion. These strains would then represent the epidemiologically relevant strains in the US and the diversity of fHbp being expressed. The

fHbp variants expressed are not homologous to the vaccine components. The fHbp variants expressed (A22, A56, B24, B44) are not homologous to the vaccine components.

The primary endpoints include the proportion of subjects achieving ≥ 4 -fold increase in hSBA titer from baseline to post-dose 3 for each of the 4 test strains (minimum response = hSBA titer of $\geq 1:16$); the proportion of subjects achieving post-dose 3 hSBA titer $\geq 1:8$ ($1:16$ for the A22 expressing strain) for all 4 test strains (composite); and pre-specified thresholds for the lower bound of the 95% CI for each primary endpoint. Very stringent endpoints will define this vaccine that, in all likelihood, will provide broad protection.

The clinical development plan for rLP2086 was designed for the evaluation and implementation of this vaccine in the adolescent and young adult age groups. A number of studies have been conducted in the US, Europe, and Australia. In addition to large safety and immunogenicity studies and clinical lot consistency, studies were conducted to evaluate the vaccine when given concomitantly with recommended adolescent vaccines. Some studies are completed, while others are ongoing.

At the time of the university outbreaks and toward the end of 2013, a significant body of data was available. Although designed for different purposes, the following three studies were conducted using validated strains expressing those antigens, which resulted in the generation of important hSBA data:

Study Description	Age in Years	Design (Control)	Bivalent rLP2086 (120 µg)	Control Only	Status
Safety & Immunogenicity With Concomitant Gardasil® (US)	≥ 11 to <18	Observer-blinded (Gardasil®)	1982	501	Completed
Safety & Immunogenicity 2-Dose & 3-Dose Schedules (EU)	≥ 11 to <19	Single-blinded (saline at some visits)	1696	16	Completed
Safety & Immunogenicity With Concomitant Repevax® (EU)	≥ 11 to <19	Single-blinded (Repevax®)	374	378	Completed

In fact, those protocols were amended to include the licensure endpoints and it was possible to move forward with the BLA submission to the FDA for the accelerated approval and priority review of bivalent rLP2086 on June 16, 2014. As announced earlier, Trumenba® was approved on October 29, 2014. Licensure was based on clinical data from pivotal trials involving over 4500 subjects, demonstrating an acceptable safety profile, and hSBA responses that meet pre-specified endpoints. Because this was an accelerated approval, there are conditions. Pfizer is required to submit confirmatory data from additional subjects in ongoing studies post-approval.

Trumenba® is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. Trumenba® is approved for use in individuals 10 through 25 years of age. Approval of Trumenba® is based on demonstration of immune response, as measured by serum bactericidal activity against four serogroup B strains representative of prevalent strains in the US. The effectiveness of Trumenba® against diverse serogroup B strains has not been confirmed. Trumenba® is administered on a 0-, 2-, 6-month schedule.

Dr York reviewed the hSBA results from three pivotal trials, which demonstrated that bivalent rLP2086, administered as a three doses series, consistently elicited bactericidal responses that were above the accepted correlate of protection (hSBA ≥ 4) and that met the specified

licensure immunogenicity endpoints. A high proportion of subjects achieved a four-fold rise in hSBA titer against each of the four test strains (range: 75-95%) when bivalent was administered alone or concomitantly with HPV4 or Tdap-IPV, a vaccine approved and used outside the USA in adolescents. Greater than 80% of subjects demonstrated an hSBA titer ≥ 8 for all four test strains (composite endpoint).

In summary, the hSBA responses to Trumenba[®], the bivalent rLP2086, elicited hSBA responses in completed trials that met all of the pre-specified primary licensure endpoints agreed upon with the FDA and other regulatory agencies. The licensure criteria are designed to demonstrate vaccine-elicited responses that have the potential to provide broad protection against diverse MenB strains is well-illustrated in the exploratory analysis of recent university outbreaks. There was a significant 4-fold rise, which was highest against the isolates from University B. The percent response is very similar to what was observed in the pivotal studies. The response against those in University A was similarly very high.

The safety data in over 4500 subjects were submitted to FDA. This is across seven clinical trials, demonstrating an acceptable safety profile. The majority of local and systemic events were mild to moderate in severity after each vaccination and were transient. The most common AEs were pain at the injection site, fatigue, headache, muscle pain, and chills. There was no pattern of potentiation with progressive dosing. The vaccine has demonstrated an acceptable profile when administered with HPV4 or with Tdap-IPV, which is not a US-licensed product. The rates of SAEs were comparable between the vaccine recipients and controls, 1.7% versus 1.6%, in four controlled trials.

In summary, Trumenba[®] was designed to provide broad protection against meningococcal serogroup B strains. The vaccine is composed of two fHbps, one from each fHbp subfamily. fHbp is a conserved meningococcal virulence factor. Trumenba[®] has been evaluated in adolescents and young adults who are at increased risk of meningococcal disease. hSBA data from pivotal studies met pre-specified endpoints established with the FDA, predicting protection against prevalent meningococcal serogroup B strains causing disease in the US. A favorable safety profile was demonstrated when bivalent rLP2086 was given alone or with concomitant vaccines (HPV4 or Tdap-IPV). The full public health potential of Trumenba[®], an FDA-licensed serogroup B vaccine, will only be realized with vaccination strategies that go beyond outbreak control and target prevention in US populations at increased risk of meningococcal disease.

Discussion Points

With respect to the Pfizer vaccine, Dr. Karron wondered if there were any data on achieving protective levels after a single dose, for example, in an outbreak situation. She also asked about duration of protection and whether any data are available on concomitant administration with ACWY vaccines.

Regarding protective levels after a single dose, Dr. York responded that the data show a 35% to 50% response rate after a single dose. The study conducted in the EU to assess two versus three doses showed that a high percentage of subjects achieved a titer of greater than 1:8 against the four strains. Looking at several 2 dose schedules, the responses were quite significant. However, these would not have met the FDA criteria for licensure. Regarding duration of protection, Pfizer is currently generating persistence data. Pfizer can present those data to ACIP as soon as they are available. A study will be completing soon that assesses a

number of concomitant vaccines. Those data will be available in the next couple of months and will be provided to the WG.

Mr. Wassil responded that Novartis has demonstrated persistence for up to 23 months, which is the longest data they have in those 11 to 17 years of age. In addition, data were collected in Study V72_29 in the UK university students that went through 11 months, which were similarly robust. Novartis also plans to study concomitant use with ACWY, but does not currently have those results.

Dr. Reingold asked whether anything is known about the effects of either vaccine on carriage.

Mr. Wassil responded that it is very difficult in the pre-licensure setting to demonstrate an impact on carriage. In many cases, it is necessary to immunize a broad population to interrupt transmission. That said, Novartis tried to exhibit some demonstration of carriage reduction in the UK in university students by giving a thousand doses of 4CMenB to one group and another thousand with a control. While the primary endpoint was not met (e.g., demonstrating carriage reduction one month after completion of the 2-dose series), follow-up between 3 and 12 months showed a statistical reduction overall in carriage of about 26% percent in ACWY and B isolates.

Dr. York replied that Pfizer has not assessed the impact of its vaccine on carriage, though consideration is being given to the possibility. The impact on carriage pertains to new acquisitions. It is very difficult to set up a clinical trial to ascertain reductions in acquisition of new carriage.

Ms. Pellegrini pointed out that this is another adolescent vaccine with three doses in less than a year, which may or not be aligned with the recommendations for the other adolescent vaccines. As the parent of two teenagers, she emphasized the difficulty of getting a teenager to the doctor for a well-visit once a year. With that in mind, she made a plea for the alignment of the schedules to the maximum extent possible. It is known that the completion rates for current meningitis and HPV series are dismal. This issue must be examined thoughtfully, or the same situation will occur with the MenB vaccine.

Dr. Byington (AAP) asked whether Novartis has any data on cross-protection with other serotypes other than type B.

Mr. Wassil replied that Novartis has limited data on protection demonstrated in an SBA assay for non-B serogroups. There is a publication on serogroup X, where they were able to cover the clonal outbreaks in Africa. They have also done work in the UK, Germany, France, Brazil, and Argentina to assess some non-B strains. Coverage of those is between 30% to 100%.

Dr. York clarified that fHbp is a meningococcal protein and it is not specific just to MenB. While Pfizer has pre-clinical exploratory analyses that show that immune sera can be active against the other serogroups, this vaccine was developed for prevention of MenB.

Dr. Baker (IDSA) requested further details about which other capsular serogroups. She noted that she asked because there are 13 capsular types, but many fewer are prevalent in terms of the cause of human disease everywhere in the world, especially in the US.

Dr. York said the gene is found in all of them (ACWY). Pfizer has some data that show protection against C and Y, and continues to assess other serogroups as well. As Mr. Wassil said, a number of studies have been conducted to assess activity toward different serogroups.

Mr. Wassil added that when the capsular antigen is removed, it results in something very similar to MenB. It is a strain-specific demonstration of a response. Novartis has conducted testing in Argentina, for instance, and coverage was exceptionally good for W. It is not clear whether that means that the vaccine will impact W circulating in the US. They would have to perform the same SBA analysis. The reason Novartis is hesitant to give actual information about what is pertinent in the US environment is that non-B serogroup strains originating in the US have not been tested. For instance, an outbreak of W is occurring in the UK presently. Novartis tested it and found that the vaccine covers that exceptionally well. That has to be answered on a specific basis.

Dr. Whitely-Williams (NMA) asked whether any data are available on immunocompromised persons, particularly HIV patients with functional asplenia or any plans to conduct those studies.

Dr. York replied that Pfizer has no data at this time, though they have considered the possibility of following up with those studies as well.

Mr. Wassil responded that Novartis has not studied HIV patients. As a post-licensure commitment to Europe, they have completed a study in people with asplenia and complement-deficient individuals. The results of that study are expected soon.

Dr. Pickering said he could not find syncope, the most common AE in adolescents, and wondered whether there were any data on this. In addition, he recalled the unpleasant surprise with the quadrivalent vaccine when it was believed that only one dose would be adequate but it was later determined that two would be needed. He asked whether any modeling could be done to predict the duration of protection for 2 versus 3 doses.

Dr. York responded that regarding syncope, the most common AE they observed was pain at the injection site. Pfizer has not done any modeling in that context. They have done modeling regarding the potential impact and estimated times of depletion of antibody over time, but have not done that to predict the actual information since they do not have the persistence data at this point.

Mr. Wassil replied that Novartis has distributed over 1 million doses and they know that over 100,000 doses have been administered. A few cases of syncope and vasovagal reactions have been reported in a post-licensure setting. In terms of modeling, they have 23 months of persistence data in Chile and 11 months in the UK. Novartis has been able to do some modeling, which depends upon the protection of these indicator strains and not all of the strains circulating. Based upon that, Novartis estimates between 6 to 8 years of persistence with this vaccine. However, the caveat is that this is heavily based on modeling.

An inquiry was posed regarding whether there are any data about safety and immunogenicity, and how long the protection will last in children when it is given concomitantly with a routine childhood immunization? The quadrivalent meningococcal conjugate vaccine was introduced for children and adults four years ago. Since that time, all cases of meningitis have been in children less than six months and it has been type B.

Dr. York replied that the Pfizer vaccine was studied in persons 10 through 25 years of age. They have assessed concomitant administration with the routine immunizations that are given in adolescents. They anticipate having data on Adacel[®] and MCV4 very soon.

Dr. Loehr (AAFP) asked whether he understood correctly that Pfizer's vaccine has been FDA-approved for general use and Novartis's vaccine has been approved for special situations. He also wondered whether both were used at Princeton and University of California Santa Barbara, or if that was only the Novartis vaccine.

Mr. Wassil clarified that the Novartis vaccine has not been approved for use by the FDA. 4CMenB was used in the Princeton and University of California Santa Barbara outbreaks under a CDC-sponsored expanded-access IND. Technically, it was part of a clinical program.

Dr. York clarified that Pfizer's vaccine, Trumenba[®], was just licensed the previous day for use in the US.

Epidemiology of Serogroup B Disease in the US

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. MacNeil described the current epidemiology and burden of serogroup B meningococcal disease in the US, with a focus on adolescents and young adults and college students, followed by a brief review of the groups at high risk for serogroup B meningococcal disease.

There are two sources of surveillance data for meningococcal disease in the US. The first is the Active Bacterial Core surveillance system (ABCs). ABCs is an active laboratory and population-based surveillance system that collects data on culture-confirmed cases of meningococcal disease in 10 states. Cases in the ABCs sites can be projected to the US population to estimate incidence. The second is the National Notifiable Diseases Surveillance System (NNDSS), which is a passive surveillance system to which all states and territories report data for all nationally notifiable diseases. NNDSS captures information on cases, including cases confirmed by PCR. However, serogroup and outcome information has historically been limited. Since 2005, serogroup and outcome information in NNDSS has been supplemented by data from state health departments and ABCs to improve data quality.

In the US, the incidence of meningococcal disease is currently at a historic low. In 2013, 564 cases were reported to NNDSS among persons of all ages. Declines in incidence have been observed for all of the serogroups, including serogroup B, which is not included in the quadrivalent vaccines. In addition, despite the increase in coverage with quadrivalent vaccine among adolescents, much of the decline in incidence occurred prior to high levels of coverage in adolescents.

The incidence of meningococcal disease is highest among children less than one year of age. In that age group, 67% of disease is caused by serogroup B. There is a smaller peak in disease incidence among adolescents and young adults. In that age group, approximately 40% of disease is caused by serogroup B. Based on incidence of meningococcal disease by serogroup for adolescents during two time periods, 2005 to 2007 and 2010 to 2013, incidence has declined for serogroup B and serogroups C and Y combined in more recent years (2010 to 2013 vs. 2005

to 2007). However, serogroup B disease now causes about the same amount of disease as serogroups C and Y in this age group. The change in the proportion of serogroups C and Y disease among adolescents is likely the result of quadrivalent vaccine use in this age group, as this has not been observed in age groups not recommended routinely for vaccination. It is estimated that serogroup B cases in 11 through 24 year olds have declined from 161 per year in the last high-incidence years (1997-1999) to approximately 48 to 56 cases annually in the recent low-incidence years (2010-2012). The case-fatality ratio from serogroup B is 12.5%, which is slightly lower than for serogroups C and Y combined for which the case fatality ratio is 16.6%. Among adolescents and young adults, the case-fatality ratio from serogroup B is roughly half of that observed for serogroups C and Y combined.

Information on college attendance for meningococcal cases is collected through ABCs but is not collected in NNDSS. During 1999 through 2012, 29% of serogroup B cases in all 18 through 23 year olds reported through ABCs attended college. That proportion can be applied to serogroup B cases reported through NNDSS in this age group to estimate the number of cases of meningococcal disease occurring in college students nationwide. In the US in 2012, approximately 61% of young adults completed high school and enrolled in college. Therefore, it is estimated that there are approximately 16.6 million college students aged 18 through 23 years in the US. From 2008 to 2012, there were approximately 11 cases of serogroup B meningococcal disease in college students annually, with one death in this group. This is out of 37 cases and 2 deaths among all 18 through 23 year olds. The incidence of serogroup B disease in college students during the most recent years of 2008 to 2012 was 0.07 per 100,000 compared to an incidence of 0.14 per 100,000 among all 18 through 23 year olds. While the incidence and number of cases of serogroup B meningococcal disease among college students has continued to decline, there have been five serogroup B clusters or outbreaks on college campuses in the last five years. These outbreaks have been described to ACIP previously. They had between 2 and 13 cases per outbreak and have lasted from a few days to nearly two years. Fortunately, meningococcal outbreaks remain rare in the US. However, these outbreaks cause significant anxiety and are devastating to the communities in which they occur.

To summarize the epidemiology of serogroup B meningococcal disease, with widespread use of conjugate vaccine in adolescents and young adults, serogroup B now causes 40% of meningococcal disease cases in this age group. Approximately 50 cases occur among 11 through 24 year olds, with one-third of cases among 18 through 23 year olds occurring in college students. While most serogroup B cases are sporadic, even in college students, recent outbreaks on college campuses have been due to serogroup B.

Three main groups are considered to be at high risk for meningococcal disease: 1) those with medical conditions that place them at increased risk, including those with persistent complement component deficiencies and functional or anatomic asplenia; 2) microbiologists; and 3) outbreak at-risk populations. While these groups are all currently recommended for vaccination with quadrivalent vaccines, they remain at risk for serogroup B meningococcal disease.

Persistent or genetic deficiencies in the common complement pathway are well known to increase risk for meningococcal disease. These deficiencies are rare and only affect about 0.03 percent of the US population¹. Individuals with persistent complement component deficiencies are at up to 10,000-fold increased risk for developing disease and often develop recurring infections². Eculizumab (Soliris[®]) treatment has not been previously included in the high-risk vaccination recommendations for meningococcal disease, but it functionally creates a complement deficiency by binding the C5 and inhibiting the terminal portion of the complement

cascade. Several individuals in the clinical trials for Soliris® have reportedly developed meningococcal infections despite prior vaccination with quadrivalent vaccine³ [P Densen. Complement deficiencies and meningococcal disease. *Clin Exp Immunol.* Oct 1991; 86(Suppl 1): 57-62; Cohn et al. Prevention and Control of Meningococcal Disease. *MMWR.* March 22, 2013; 62 (RR-2); http://soliris.net/sites/default/files/assets/soliris_pi.pdf].

Persons with functional or anatomic asplenia also appear to be at increased risk for meningococcal disease. However, those data are less compelling than their risk for pneumococcal disease¹. This group includes persons with sickle cell disease, which affects about 90,000 to 100,000 persons of all ages in the US². In asplenic persons, the case-fatality ratio for meningococcal disease is elevated³. [Cohn et al. Prevention and Control of Meningococcal Disease. *MMWR.* March 22, 2013; 62 (RR-2); <http://www.cdc.gov/ncbddd/sicklecell/data.html>; Updated recommendations for the use of meningococcal conjugate vaccines. *MMWR.* January 28, 2011; 60(3): 72-76].

Microbiologists who work with *Neisseria meningitidis* are also at increased risk for disease¹. A high case-fatality ratio has been observed among microbiologists who have developed meningococcal infections, likely because of increased exposure to high concentrations of organisms and highly virulent strains. The majority of cases among microbiologists have occurred in people who were not using respiratory protection at the time of exposure, and these were not limited only to research microbiologists who routinely work with meningococcal isolates. There are an estimated 100,000 clinical microbiologists and about 400 research microbiologists who routinely work with *Neisseria meningitidis* in the US [Cohn et al. Prevention and Control of Meningococcal Disease. *MMWR.* March 22, 2013; 62 (RR-2)].

The final high-risk group includes people in the at-risk group during a meningococcal outbreak. Fortunately, meningococcal outbreaks are rare and cause only about 2% to 3% of US cases¹. However, as an example of the increased risk for meningococcal disease in the recent serogroup B outbreaks at college campuses, at Princeton University, there was a 1400-fold increased risk for meningococcal disease. Roughly 7500 individuals were recommended for vaccination with serogroup B vaccines in that outbreak. In the recently published guidance for serogroup B outbreaks in institutional settings, the threshold for vaccination has been defined as 2 cases in institutions less than 5,000 persons and 3 cases in institutions with more than 5,000 people² [National Notifiable Diseases Surveillance System; <http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf>]. The following table summarizes the risk groups just discussed and includes available data on cases that have occurred in each of these groups:

Summary of Groups at Increased Risk for Meningococcal Disease			
Group	Estimated persons aged ≥10 years	Risk	Cases
Persistent complement component deficiencies	0.03% ¹ ~80,000 persons	<ul style="list-style-type: none"> Up to 10,000 fold increased risk² High risk of recurrent disease² 	6 cases ABCs (none serogroup B)
Anatomic or Functional Asplenia (including sickle cell)	Sickle cell ~90,000-100,000 (all ages) ³	<ul style="list-style-type: none"> Risk not well defined² Higher risk of mortality (40-70%)³ 	11 cases ABCs (2 serogroup B)
Microbiologists	~100,000 clinical; 400 research	<ul style="list-style-type: none"> 13/100,000² Higher risk of mortality² 	22 cases worldwide 1985-2014 ⁴
Outbreak at-risk populations	60,000 in 5 university outbreaks	Up to 1400 fold increased risk (Princeton)	32 cases combined

¹P Densen. Complement deficiencies and meningococcal disease. *Clin Exp Immunol.* Oct 1991; 86(Suppl 1): 57-62.
²Cohn et al. Prevention and Control of Meningococcal Disease. *MMWR.* March 22, 2013; 62 (RR-2)
³<http://www.cdc.gov/ncbddd/sicklecell/data.html>
⁴Borrow et al. Safe laboratory handling of *Neisseria meningitidis*. *Journal of Infection* (2014); 68: 305-312.
⁵Updated recommendations for the use of meningococcal conjugate vaccines. *MMWR.* January 28, 2011; 60(3): 72-76.

Excluding the at-risk population in outbreaks, it is estimated that there are less than 300,000 individuals who fall into these high-risk groups. Although only a handful of cases have been documented in ABCs or the published literature, these groups are known to be at high risk for meningococcal infection and are currently recommended to be vaccinated with meningococcal conjugate vaccines. However, they remain at risk for serogroup B disease.

In conclusion, the incidence of meningococcal infections is declining, including for serogroup B. In recent low-incidence years, approximately 50 cases of serogroup B meningococcal disease occurred in adolescents and young adults each year. In addition, persons in high-risk groups who are recommended for vaccination with quadrivalent meningococcal vaccines remain at risk for serogroup B meningococcal disease.

Considerations for Use of Serogroup B Meningococcal Vaccines in the US

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National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Patel noted that the Meningococcal WG has been discussing serogroup B meningococcal (MenB) vaccine issues on work group calls, and provided a summary of some key points regarding these vaccines and the work group's considerations for use of MenB vaccines in the US.

Development of MenB vaccines has been challenging. The polysaccharide capsule is the vaccine target for MenACWY vaccines, but it is poorly immunogenic for MenB because of antigenic similarity to human neuronal cells. MenB vaccines that target other antigens such as outer membrane vesicles have been used to control several MenB outbreaks in the past, including a large epidemic in New Zealand in the early 2000s. However, these vaccines are strain-specific and provide limited cross-protection with heterologous strains, have a limited duration of protection, and have limited efficacy in younger children. Ideally, vaccine targets would require antigens to be an essential gene, be immunogenic, have relatively low diversity, and be surface-exposed.

Recently, several outer membrane proteins that are found across all meningococcal strains regardless of serogroup have been identified that generally meet these criteria. fHbp allows the bacteria to evade complement-mediated lysis. fHbp is classified as either Subfamily A (Variant 2, 3) or Subfamily B (Variant 1). NHBA promotes bacterial survival in the blood, and NadA allows the bacteria to adhere to and invade epithelial cells. Although these proteins can be found on the majority of MenB strains, they are antigenically diverse and can, therefore, impact vaccine effectiveness.

There are two MenB vaccines for persons 10 through 25 years of age being considered in the US. As mentioned in the earlier presentations, rLP2086 is manufactured by Pfizer and is a 3-dose series administered at 0, 2, and 6 months. It contains both subfamilies of fHbp and was licensed by FDA on October 29, 2014 as Trumenba[®]. 4CMenB, or Bexsero[®], which is manufactured by Novartis, is a two-dose series administered at 0 and 1 to 6 months. It contains fHbp Subfamily B (Variant 1), Nhba, NadA, and PorA 1.4, which is the same PorA type as the OMV vaccine used to control the New Zealand epidemic. It was licensed in Europe, Australia, and Canada in 2013 for persons \geq 2 months of age, and it was administered to almost 17,000

participants under an expanded-access IND protocol to control two recent university outbreaks in the US. In light of these outbreaks, it was granted a priority review designation, with an announcement regarding licensure expected by early 2015.

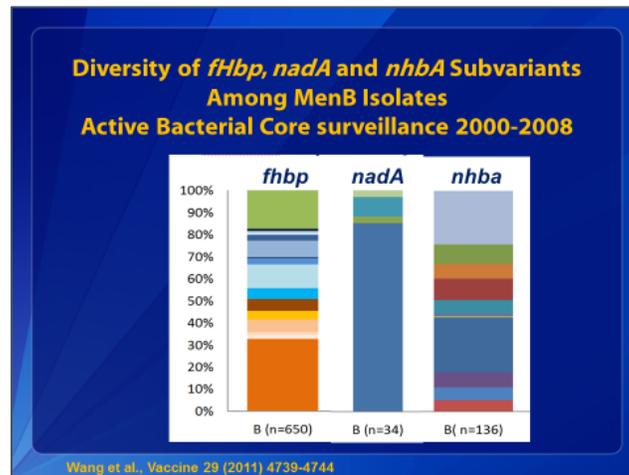
Because of the low incidence of meningococcal disease in the US, pre-licensure trials using clinical outcomes would require very large sample sizes and, thus, are not feasible. hSBA has been shown to correlate with protection against meningococcal disease and is based on studies conducted in the 1960s that demonstrated that bactericidal antibodies were protective against invasive serogroup C disease in military recruits. Bactericidal antibodies in persons immunized with OMV vaccines during various MenB outbreaks also correlated with protection. Based on these data, hSBA was established as the serologic marker to infer protection with MenB protein vaccines during the 2011 VRBPAC meeting.

However, there are several challenges in assessing immunogenicity with MenB vaccines. First, evaluating clinical efficacy in higher incidence countries would not be appropriate for licensure in the US because the molecular epidemiology differs between countries. Second, the measurement of hSBA is assay-specific and requires validation each time a parameter such as strain or antigen has changed. Because of the antigenic diversity among MenB strains, bactericidal activity against multiple strains is needed to evaluate antigen-specific responses and address cross-protection with heterologous strains. However, the number of strains that can be tested is limited by hSBA methodology, which would require large volumes of sera and identification of a complement source for each strain tested.

Because the vaccine targets and the number of vaccine targets differ between the two vaccines, selection of the four primary strains to assess immunogenicity was performed differently for each vaccine. For 4CMenB, strains were selected to evaluate immunogenicity to each of the four antigens individually using individual human sera. For rLP2086, strains were systematically selected to assess immunogenicity using individual human sera from a representative collection of circulating strains in the US. The differences in the strains selected and the method in which they were selected for each respective vaccine is important to consider when interpreting immunogenicity data. A second key difference in how immunogenicity was assessed for the two vaccines is the primary endpoints. These primary endpoints were presented earlier by the manufacturers. For 4CMenB (Bexsero[®] by Novartis), the primary endpoint was the proportion of subjects with hSBA titers $\geq 1:4$ or $\geq 1:5$. Of the subjects, 73% to 100% demonstrated protective titers. Titers decreased by 5% to 25% at two years post-vaccination depending on the antigen that was tested and the population evaluated. For rLP2086 (Trumenba[®] by Pfizer), the primary endpoint was the proportion of subjects with hSBA titers at a four-fold increase from baseline (minimum titer $\geq 1:16$), and a composite endpoint of hSBA $\geq 1:8$ or $1:16$. Of the subjects, 75% to 100% demonstrated protective titers following 3 doses. No long-term immunogenicity data are available for rLP2086. Recognizing that the primary endpoints differ for each vaccine is also important to consider when interpreting immunogenicity data in comparing vaccines.

The polysaccharide capsule is highly conserved among strains within each serogroup. Therefore, vaccines that target the capsule (quadrivalent meningococcal vaccines) typically do not require assessment of breadth of coverage. Because the vaccine targets for MenB vaccines are antigenically diverse within circulating MenB strains in the US, a multi-factorial approach can be helpful in estimating coverage. This includes determining the presence or absence of the gene, genetic sequences, level of expression of the antigen, and bactericidal activity by hSBA.

In a study by Wang, the first two factors were assessed (e.g., presence or absence of the gene and the genetic sequences). Through ABCs, 650 MenB isolates were collected from 2000 to 2008 and were sequenced for the three different vaccine targets: fHbp, NadA, and Nhba. The following graphic illustrates the degree of genetic diversity in the subvariants circulating in the US, particularly for fHbp and Nhba:



Genetic sequencing showed that all MenB isolates contained fHBP and that 59% were Subfamily B (Variant 1), which is contained in both vaccines, and 41% percent were Subfamily A (Variant 2, 3), which is contained only in rLP2086. NadA, which is included in 4CMenB, was present in only 39% of all MenB isolates. Because NadA was found in less than 10% of isolates that were fHbp Subfamily A (Variant 2, 3), which is not included in the vaccine, based on this analysis, NadA would only increase coverage for 4CMenB from 59% to 63%. Nhba is highly diverse and is found on all MenB isolates, but, as presented earlier, elicits lower titers in bactericidal antibodies. PorA 1.4, which is also included in 4CMenB, was found in less than 5% of MenB isolates [Wang et al., *Vaccine* 29 (2011) 4739-4744]. In this study, only genetic sequencing was assessed. The study did not measure the degree of protein expression or bactericidal activity for each of the isolates.

Assessing breadth of coverage can be complicated and was performed differently for each vaccine. Differences in how breadth of coverage was estimated by the manufacturers is important in understanding how well each vaccine will protect against endemic disease. For rLP2086, fHbp sequence analysis and measurement of surface expression by flow cytometry was performed for an epidemiologically representative collection of over 1200 MenB strains, of which 432 were collected from ABCs surveillance sites. This analysis demonstrated variability between subfamilies as well as surface expression of fHbp. In a subset of isolates for which bactericidal activity was assessed, isolates with moderate or high-level expression of fHbp were predictive of bactericidal activity; whereas, there was lower correlation among isolates with low expression of fHbp [Jiang et al., *Vaccine* 28 (2010) 6086-6093].

Novartis used a different approach to assess breadth of coverage of 4CMenB. Because there are multiple antigens contained in the vaccine, there are limitations on how many strains can be tested by hSBA for the reasons mentioned previously. The meningococcal antigen typing system is a sandwich ELISA that was developed to measure both cross-reactivity with vaccine antigens as well as the level of expression of each antigen to predict bactericidal activity against a broad number of strains. MATS was previously bridged to hSBA in a subset of antigenically

diverse strains and was found to be greater than 80% predictive of bactericidal activity when one antigen was expressed above a certain threshold, and greater than 90% when at least two antigens were expressed above a certain threshold. Based on an analysis of over 400 isolates collected through ABCs, 4CMenB is estimated to cover 91% of circulating strains in the US [Donnelly et al., *PNAS* (2010) vol. 107, no. 45].

In summary, two MenB vaccines are available in the US: rLP2086, which was recently licensed as Trumenba[®], and 4CMenB, which is currently undergoing priority review by FDA. A serologic marker was used to infer protection against MenB disease. Demonstration of breadth of coverage against diverse strains will be critical for evaluating vaccine effectiveness. There could be potential differences in immunogenicity and breadth of coverage between the two vaccines due to their different vaccine targets.

Regarding WG considerations for use of MenB vaccines in the US, as Ms. MacNeil presented earlier, rates of meningococcal disease have reached historic lows and are decreasing for all serogroups. Vaccination with MenACWY conjugate vaccine is recommended for adolescents 11 through 12 years of age, with a booster at 16 years of age. Increasing coverage with these vaccines has contributed to decreasing rates of disease among adolescents. However, MenB disease continues to contribute to about 40% of meningococcal cases, with 50 cases reported annually among adolescents in recent years.

There are a number of challenges to keep in mind when considering use of MenB vaccines in the US. First, breadth of coverage has only been estimated. Actual breadth of coverage is unknown. Although there are some data for 4CMenB, duration of protection and impact on carriage is unknown. The potential impact of vaccine pressure on circulating strains will be unknown until these vaccines are used more broadly. The multi-dose schedules required for both vaccines make implementation challenging. Again, it is important to note that the burden of MenB disease is low and not all cases will be prevented by vaccination.

The WG has been discussing a number of different options for use of MenB vaccines to address the immediate need to protect high-risk groups. The WG is considering vaccination of persons with medical conditions who are at high risk for meningococcal disease such as persistent complement component deficiencies or anatomic or functional asplenia, microbiologists, and for use in outbreak response. The WG also has been reviewing available data and discussing options for routine recommendations for expanded groups.

Although the vaccines have been reviewed or are currently undergoing review through an accelerated pathway, additional data are still needed for both vaccines to inform policy decisions. This includes duration of protection; immunogenicity against additional strains to evaluate breadth of coverage, safety, and immunogenicity of concomitant vaccination; high-risk groups as well as other age groups; and additional safety data. A number of these studies are ongoing and will be reviewed by the work group once these data are available.

The WG has prioritized considerations for vaccination of high-risk groups in persons ≥ 10 years of age. As presented earlier, persons with high-risk medical conditions and microbiologists account for less than 300,000 people in the US. Based on the interim guidelines for use of MenB vaccines in institutional settings, vaccination would have been recommended for all five MenB outbreaks reported on college campuses over the past five years for approximately 60,000 people. The overall goal will be to align the high-risk and outbreak recommendations for both MenB and MenACWY vaccines.

Thus, the current plan for the February 2015 ACIP meeting is to present GRADE for high-risk groups and propose language for use of MenB vaccines in persons ≥ 10 years of age with high-risk medical conditions, microbiologists, and outbreaks for a potential vote. Additionally, for the June 2015 and October 2015 meetings, the WG will review the evidence for expanded target groups, which includes GRADE and economic and impact analyses, and will present the updated outbreak guidelines for all serogroups.

In conclusion, considerations regarding use of MenB vaccines in the U.S. will be complex. Additional data following licensure will help to inform policy decisions. The WG will continue to review data on MenB vaccines as it becomes available, and will engage in discussions on use of these vaccines for expanded groups. Dr. Patel requested feedback from the full membership on the following topics:

- Feedback on a two-tiered approach
 - High risk recommendation in February 2015
 - Continued discussions regarding use of MenB vaccines in broader target groups

- Additional data ACIP would like to have presented at future meetings

Discussion Points

Dr. Temte thanked Ms. MacNeil and Dr. Patel for their very nice, well-organized, succinct presentations.

Since Bexsero is licensed elsewhere starting at two months of age, Dr. Harrison wondered about the plans for licensure in the US down to that age range.

Mr. Wassil replied that Novartis has decided that sufficient progress has been made on an ABCWY vaccine, and he previously showed the of Phase II studies for different formulations. Novartis is trying to go forward with an ABCWY vaccine in infants in the US, but that is several years away.

Dr. Baker (IDSA) emphasized that the current serogroup B-specific incidence is 0.1 per 100,000. Yet in infants less than one year of age, it is 1.5 per 100,000. She asked whether there are any data for children less than one year of age for the first six months of life and whether any thought had been given to maternal immunization. She would assume a pregnant microbiologist would be vaccinated. She also wondered about travelers to serogroup B hyperendemic or epidemic areas.

Ms. MacNeil replied that there are data in children less than six months of age, which were presented several ACIP meetings ago. A lot of the disease is in the younger infants. She thought Dr. Baker's question about maternal immunization was a great one. Consideration has not been given to travelers to serogroup B hyperendemic or epidemic areas at this point.

Dr. Belongia asked about the considerations for potential use in microbiologists who are over 25 years of age, given that the current licensed recommendation is for those 10 through 25 years of age.

Dr. Patel replied that this pertains to the granularity of the microbiologist recommendation that the WG will be discussing. At this point, the WG is suggesting that the recommendation would be individuals ≥ 10 years of age. The difference is that the doses change for younger individuals and the immunogenicity is different. It is expected that the immunogenicity would be similar for the older age groups.

Dr. Byington (AAP) asked whether the WG is considering a routine recommendation for college students, or a recommendation only for outbreak settings.

Dr. Patel replied that the high-risk recommendations the WG is considering for February 2015 would pertain to an outbreak response. Routine recommendations for college students and adolescents are still being discussed. The WG is still waiting for additional data. They are reaching out to non-ABCs sites, such as the MeningNet sites, to get a better understanding of college cases within other states that are not in ABCs.

Dr. Temte asked whether pricing had been established for Trumenba[®] and Bexsero[®] for the US market.

Angela Hwang (Pfizer US) responded that Pfizer's current priority has been about securing supply, which they expect shortly. Because of the rapid nature by which this approval has taken place, pricing is still being finalized. While she did not have pricing at that time, she indicated that they would have it as soon as possible and that it would be commensurate with the supply that they are advancing.

Clement Lewin (Novartis) indicated that Novartis does not discuss pricing prior to licensure, and their vaccine is not yet licensed.

Dr. Even (ACHA) indicated that because the college age group is included in the licensure, the first question she will receive in the college health world will regard when the vaccine will be available.

Angela Hwang (Pfizer) replied that Pfizer is working as quickly as possible to advance the supply, which they expected to be available within the next two to three weeks.

Dr. York emphasized that Trumenba[®] was licensed to prevent MenB disease. The discussion of the breadth of coverage, the phylogenetic tree, and the diversity of the fHbp addressed coverage and the fact that this is a protein which is conserved and present in all MenB. Its function is to protect it against the immune system and to invade it. Pfizer moved very fast to license this vaccine, and the WG working very hard to address this. Because the vaccine was developed to prevent outbreaks, not to say that it is not beneficial to use in control, she asked whether the ACIP members would like to see data on the use of this vaccine to prevent outbreaks in universities brought forward sooner because of this acceleration and if so, what information they would need. She understood persistence data would be needed in terms of a routine, age-based recommendation, but wondered whether they would need those data to move this forward in that risk group.

Rino Rappuoli (Novartis) said if he understood the epidemiology data shown through 2013, in the age group in question there were 50 cases of meningococcus B with 12.5% mortality. However, during the last year, there were three deaths in that age group: one at Drexel, one at Georgetown, and one in San Diego. Basically, that means with a mortality of 12.5%, 300 cases will be needed to justify that mortality. He said he was not challenging the data before 2013, but in 2014, the incidence will be different because there are more deaths than projected by the epidemiology. While ACIP is proposing to look at the high-risk and outbreak control at the beginning, none of these three deaths were going to be prevented by just recommending outbreak control. He wondered whether that should be reconsidered.

Public Comment: Meningococcal Vaccines

Lynn Bozof, President National Meningitis Association (NMA)

Many of you are familiar with my son's story. He died in 1998 from meningococcal disease. There was a polysaccharide vaccine available, but unfortunately, there were no recommendations, so my husband and I did not know to have our son vaccinated. In October of 2000, ACIP voted to recommend that college students be educated that they were at increased risk for meningococcal disease and that there was an available vaccine. It was the right thing to do to protect our children. In 2005, the conjugate vaccine was recommended to prevent this disease in adolescents and teens. Again, it was the right thing to do. Later on, the booster dose was recommended to ensure that these kids maintain their protection. It was the right thing to do.

I have heard over and over from parents whose children have suffered from serogroup B disease, especially this past year. They all said the same thing, "I thought my children were protected." They all wanted the broadest protection possible. I was really thrilled yesterday to hear that the FDA had approved licensure of one of the vaccines, and I look forward to the other vaccine being licensed soon. We now have the tools to protect our children against all five serogroups. We need to do the right thing and routinely recommend vaccination. It's the right thing to do. It's what parents do. It's what society should do. We need to protect our children.

I also wanted to alert you to a new activity that the National Meningitis Association (NMA) is conducting. We're going to convene a roundtable that includes a cross-section of meningococcal disease advocates, including survivors, family members, college educators, infectious disease specialists, and any others who have a unique perspective and knowledge about meningococcal disease. Our goal is to prevent the real-life impact of this disease and to give voice to the concerns and viewpoints of those who have been infected. We hope to have a report to share with the ACIP before the February meeting. Thank you.

Stephen and Beverly Ross National Meningitis Association (NMA)

My name is Stephen Ross and this is my wife, Beverly. We're here today with the National Meningitis Association, and we have no conflicts. We're the parents of Stephanie Ross, and I hope her name still rings a bell with you. She was a Drexel University student who died after contracting serogroup B meningococcal in March. She went to bed early one Sunday night because she was feeling tired, and only a few hours later, she was fighting for life. It was a battle she was destined to lose. She was just 19 years old. She was an intelligent young

woman who was attending Drexel University on a Ben Franklin Scholarship. She was well-liked at Drexel, as shown by the busload of students who traveled across the vast state of Pennsylvania the weekend before finals to say goodbye to her. She also went out of her way to assist anyone who asked for help and even some who didn't. She was quickly growing into a leadership role with her Phi Mu sorority sisters. In talking about her, we always like to share a quote that was posted on the Websites that she created before passing in connection with a fundraiser for the Children's Hospital of Philadelphia. It said, "Thank you for always living your life the way it was supposed to be lived: full of love, laughter, and kindness. It's not just friends, but strangers as well."

Since Stephanie's passing, at least two more college students have died from the serogroup B disease. When will it stop? We need to say, "Enough is enough." As a percentage of all students that populate our country's college campuses, we realize that these deaths represent a small number. But when the student is one of yours, any number above zero is unacceptable, especially if it could've been prevented. Parents have lots of things to think about when they send their children off to college. We shouldn't have to worry about this disease. Let's do the right thing to help protect our children from this devastating bacteria. We seem to have the means to stop the spread of this disease, as evidenced by the fact that no additional cases have been reported from the Princeton campus since the use of the serogroup B vaccination there. We don't want any more parents to receive a call like we did when you hear that your child has died from contracting serogroup B meningitis.

Now that the FDA has licensed the first of the serogroup B meningococcal vaccines, we hope that you will recommend them for adolescents and young adults. At the very least, they should be recommended for college students because they seem to be the largest group at risk. Like us, many parents and students have mistakenly believed that the previously licensed vaccines protected them against all the serogroups that can affect our children. In the coming weeks, several groups associated with Drexel University will be sending letters supporting recommendation for college-aged adults. Some of them will be from Stephanie's classmates who would like nothing more than to be protected from the bacteria that took the life of their dear friend. They want to be able to win the battle over the disease that Stephanie could not conquer. We are here on their behalf. Now, on behalf of her sister, Jacqueline, who now is an only child and a freshman at one of the largest universities in the US, it will be a tragedy, like Stephanie's death, to see the vaccines approved by the FDA but not widely recommended. Thank you for the opportunity to address you.

Frankie Milley
National Executive Director
Meningitis Angels

You've shared stats today, and I want to share just a quick stat with you. My mother's twin brother died from diphtheria. Her father died from tetanus. Her cousin died from influenza in the big outbreak in the early 1900s. As I grew, one of my best friends had polio and was in an iron lung. And later, he did survive. He was in a wheelchair and very crippled for the rest of his life, which was very short, I might add. My sister had chickenpox and was in the hospital for three weeks. We almost lost her. She had serious secondary infections and pneumonia from that disease. My mother died from Hib pneumonia just a few years ago. As you know, Ryan died from meningococcal meningitis. He went from perfect health to blood coming from every orifice of his body in less than 14 hours. My only child. I watched him die needlessly.

I don't share this with a lot of people, but I've been married to my current husband for almost 41 years. But before that, I was married for a year to someone just to show my mother I could. Unfortunately, out of that, I blew a scholarship to college. I said I came away with half the alphabet. I had TMJ from being slapped around, and I had HPV, which, ultimately, led to a hysterectomy, which took the part of my body that carried Ryan. It was like losing him all over.

We now have Ebola. We don't have a vaccination. I want to commend these people in this room and everybody at the CDC who has worked so hard against this disease to protect us all. You're doing a great job in keeping up, and I know you don't hear that, but I'm here to tell you, you do. If you look at meningococcal disease and you compare it to Ebola, it's really similar, only sometimes meningococcal disease works much faster. When they survive, they're left devastated.

As you move forward, there are some things I want you to consider. In our organization, we have hundreds of families across the country. We just took in a new family. Their 17 year old son died in March of this year from meningococcal B. I talked to Scott yesterday, and he was on the way to Canada today to take his other son to get vaccinated against this disease. He can't go through this again. Many parents don't have that opportunity to go to another country and get their kids immunized, so we need to be protective of that. I also want you to consider we had an outbreak in 2000 in our school district of 6500. We had 15 cases of meningococcal disease. When I called the health department at the state and told them, asked them if they knew about it, they didn't and they hadn't had any reports. They came down, and we immunized 45,000 people in three days in that outbreak. The problem was, when I went to the hospital to find out why they weren't reporting, they said "It costs money to send those specimens, and we're just not going to do it even though it's required."

So, I want you to consider that the case rate may be higher than we think it is because a lot of times when the kids are brought to the ER, they have symptoms. They're bombarded with antibiotics. We know the bacteria dies. Ryan's cause of death on his autopsy was Waterhouse-Friderichsen syndrome, which is a bilateral bleed of the adrenal glands. We know that later the sepsis from the meningococcal caused that. But I'm afraid that we're missing the actual rate of this disease in this country because we are good at our jobs or because we're not good at our jobs. That can go either way.

Finally, I just think that in a country as great as ours and the work that you've all done and the work that industry does to bring these vaccines to us—it takes years of research, development, and money. Some people research and never live long enough to see their research come to pass. We can prevent this disease. We can't prevent Ebola right now, but we can prevent this disease. Nobody in this country should die from a vaccine-preventable disease. So, moving forward, I know you've got a lot of work to do with this. I know there's still a lot of unanswered questions. I have faith in this committee right here that, at the end of the day, you're going to do the right thing and recommend this for aged 15 to 25. Please, I beg you. Let's don't go back to that day when we only vaccinate those kids living in dorms. Meningitis doesn't stop at the dorm room door. Thank you so much for your work and your kindness.

Dr. Stanley Plotkin
Vaccine Consultant

I have absolutely no conflict of interest with respect to Pfizer or Novartis. I just want to make that clear. One specific point and one general point. The specific point is, as was said, 29% of disease in adolescents occurs in college students. Obviously, that means 71% occurs in non-college students who are smoking and going to bars, et cetera. So, a recommendation for college students is, in a sense, discriminatory. The more general point is one that is an obvious, sort of a 400-pound gorilla, but I want to bring it out publicly. And that is, the two companies have spent millions of dollars to develop vaccines against what might be called a “minor disease” in terms of incidence. If these vaccines are not recommended, then this puts a pall on vaccine development for diseases that are less prevalent than the ones for which we have general recommendations. I hope you will keep that in mind for the future, because this has great implications for future vaccine development.

Dr. Carol Baker
IDSA Liaison to ACIP

Just to add to that, what vaccine-preventable disease in the US causes 10% mortality? I would second the comment about age group as opposed to college. Finally, something that I struggle with—I certainly struggled with it as Chair of the Meningococcal WG when the quadrivalent was recommended, as chair of the ACIP, and I still struggle with it. I don't have an answer, and I know you're in the hot seat in February, it sounds like. It's very difficult to know how much money we should spend for prevention of rare diseases. I think that this will increasingly trouble the CDC, ACIP members, the AAP if it's a childhood disease, and the ACP if it's an adult disease. It's very, very difficult given the past history. It's not so long ago, really little more than a decade, when vaccines were cheap for the prevention of childhood diseases. It's just a comment.

Dr. Paul Offit
Chief, Division of Infectious Diseases
Director, Vaccine Education Center
Children's Hospital of Philadelphia

You know, I felt like I've lived through this once before. When I was on the ACIP and head of the Polio Vaccine WG in the late 1990s, we made a decision to move from the oral polio vaccine to the inactivated vaccine. We did it because we knew that every year, although we'd eliminated wild-type polio from this country, we hadn't eliminated vaccine-associated paralytic polio. Now, to do that, to move from OPV to IPV costs roughly \$4 million per case prevented. But, we did it because we knew we could and because we believed we could afford it. I think, in some ways, the analogy is here. It was six to eight cases there. It's roughly 50 cases here, but I agree with Stan [Dr. Plotkin]. I think narrowing this to just a high-risk recommendation or just a college recommendation will cover roughly 50 cases that are occurring. So, I think if we really want to prevent a disease that we can prevent, then we need to make a broader recommendation. Thanks.

Dr. Jonathan Temte
ACIP Chair

I really appreciate the last three comments from Dr. Plotkin, Dr. Baker, and Dr. Offit. Just reflecting back on Slide #10 from Ms. MacNeil's presentation, the rate in college students was 0.07 cases per 100,000 and three times that for the cohort aged 18 through 23.

Typhoid Vaccines

Introduction

Barbara Mahon, MD, MPH
Medical Epidemiologist
Enteric Diseases Epidemiology Branch
National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases

Dr. Mahon reminded everyone that the current ACIP recommendation for typhoid vaccination was published almost 20 years ago, in December of 1994. The objective has been to update this recommendation because it is so long out of date. An ACIP WG on typhoid vaccines was not convened because the updated statement does not include substantive changes to the recommendations.

The following table shows the three typhoid fever vaccines included in the 1994 ACIP statement:

Vaccine	Vaccine Type	Mode of Administration	No. of Doses
Ty21a vaccine	Live, attenuated	Oral	4
Vi capsular polysaccharide vaccine	Subunit	Parenteral	1
Heat-phenol-inactivated vaccine	Inactivated whole-cell	Parenteral	2

Currently, the oral Ty21a vaccine and the parenteral Vi capsular polysaccharide (ViCPS) vaccine are still marketed and are available in the US. The heat-phenol-inactivated vaccine, which was associated with high rates of fever and other systemic reactions, was discontinued in 2000.

One of the major changes in the update is the removal of the vaccine that is no longer available in this country. In the 1994 recommendation, the statement that either oral Ty21a or parenteral ViCPS is preferable was made. This is because of the highly reactogenic nature of the heat-phenol inactivated vaccine. Vaccination is indicated for the following three groups, which have not been changed in the updated recommendation:

- ❑ Travelers to endemic countries, which continue to be the major group receiving vaccines
- ❑ Household contacts of chronic typhoid carriers
- ❑ Laboratory workers who work frequently with *Salmonella* serotype Typhi cultures or specimens

In summary, the 1994 ACIP statement is outdated. No substantive changes are proposed in the updated recommendations. The updated statement reflects changes in vaccine availability with the removal of the whole cell inactivated vaccine that is no longer available and newer data on typhoid epidemiology, vaccine efficacy and effectiveness, and vaccine safety. During this session, Dr. Brendan Jackson presented information on typhoid fever and typhoid vaccines, and a summary of the proposed updates to the typhoid vaccination statement.

Typhoid Vaccines Update

Brendan R. Jackson, MD, MPH

Medical Epidemiologist

Enteric Diseases Epidemiology Branch

National Center for Emerging and Zoonotic Infectious Diseases

Division of Foodborne, Waterborne, and Environmental Diseases

Because typhoid fever is uncommon in the US, Dr. Jackson began by providing some brief background information. The disease is caused by *Salmonella enterica* serotype Typhi. Contrary to most other *Salmonella* serotypes, humans are the only reservoir. Infection is usually acquired from food or water contaminated with human feces. The incubation period is relatively long, ranging from about 6 to 30 days. The disease usually has an insidious onset with gradually increasing fever, malaise, headache, and anorexia. Typhoid fever can be severe and deadly, particularly if untreated. Life-threatening complications include septic shock and intestinal hemorrhage and perforation.

The disease can now be treated with one of several antimicrobial agents, including the following: fluoroquinolone, beta-lactam, azithromycin, chloramphenicol, or trimethoprim-sulfamethoxazole. However, antibiotic resistance is common and increasing in many parts of the world, placing greater importance on prevention tools like vaccines¹. The case-fatality ratio for untreated disease was previously reported at 10% to 20%². However, the current case-fatality rate is less than 1% with early and appropriate antimicrobial treatment³ [¹Crump and Mintz. *Clin Infect Dis*. 2010; ²Stuart and Pullen. *Arch Int Med*. 1946; ³Bhan et al. *Lancet*. 2005].

“Enteric fever” is the broader term for both typhoid fever and paratyphoid fever. Paratyphoid fever is caused by three non-Typhi *Salmonella* serotypes: Paratyphi A, B, and C. The most common cause of paratyphoid fever is Paratyphi A, which causes disease that is clinically indistinguishable from typhoid fever¹. It is important to note that current typhoid vaccines provide little or no protection against paratyphoid fever [¹Maskey et al. *Clin Infect Dis*. 2006].

Globally, there are an estimated 20 million cases of typhoid fever annually, resulting in about 200,000 deaths per year¹. In comparison, there are an estimated 5 million cases of paratyphoid fever each year². However, in some Asian countries, paratyphoid fever caused by serotype Paratyphi A is responsible for a growing proportion of enteric fever cases, accounting for half of enteric fever cases in some areas². Multi-drug resistance, defined as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, is common for serotype Typhi. Additionally, fluoroquinolone-resistance and extended spectrum β lactamase-producing strains

are emerging problems. Growing rates of drug resistance increases the importance of vaccination as a preventive measure [¹Crump et al. Bull WHO. 2004; ²Crump and Mintz. Clin Infect Dis. 2010].

There were about 400 cases of typhoid fever reported each year from 2007 to 2011 in the US. Approximately 90% of these were travel-associated¹. Among the travel-associated cases, 80% to 85% involved travel to three countries: Bangladesh, India, and Pakistan. Use of typhoid vaccines is thought to be low among travelers, in general, with one study finding that about 20% of travelers had received vaccine². The most up-to-date vaccine recommendations for travel can be found at cdc.gov/travel. Currently, typhoid vaccine is recommended for travel to most countries in Africa, Asia, and Latin America. Since 2011, typhoid vaccine is no longer recommended for travel to certain countries in Eastern Europe and the Middle East³ [¹CDC Surveillance. <http://www.cdc.gov/national-surveillance/typhoid-surveillance.html>; ²Mahon et al. Vaccine. 2014; and ³Johnson et al. J Trav Med. 2011].

As noted earlier, two typhoid vaccines are currently available in the US. The first is Ty21a vaccine, Vivotif[®], which is a live attenuated vaccine administered as oral capsules on four alternate days over one week. Vivotif[®] is approved for persons six years of age and older, and is currently recommended every five years if continued exposure is expected. The second is ViCPS vaccine, Typhim Vi[®], which is given as a single parenteral dose. Typhim Vi[®] is approved for patients two years of age and older, and repeated dosing is recommended every two years if continued exposure is expected. No booster effect has been observed for either vaccine. Conjugate polysaccharide vaccines are available in a few countries. However, a conjugate vaccine is not licensed in the US.

Both available vaccines have moderate efficacy based on studies conducted in endemic countries¹. In a recent systematic review and meta-analysis, the Ty21a vaccine had a 2.5- to 3-year efficacy of 48% based on a single trial. In two excluded trials that did not adjust for the cluster design and may have overestimated the protective effect, efficacy was 79% at 5 years and 62% at 7 years. In the same systematic review and meta-analysis, the efficacy of the ViCPS vaccine was 69% percent at Year 1 and 59% at Year 2. The cumulative 2.5- to 3-year efficacy was 55%, based on a single study. No efficacy studies have been conducted among US travelers, but a recent study found 80% effectiveness of typhoid vaccination among this group. Note that this estimate is for any typhoid vaccination, given that the study was not able to differentiate between the two vaccines² [¹Anwar et al. Cochrane Database Syst Rev. 2014; ²Mahon et al. Vaccine. 2014].

In terms of safety, both vaccines are generally well-tolerated with low rates of adverse events based on data from trials and post-marketing studies. In the meta-analysis field trials, two events were significantly more common in vaccinees than among placebo recipients: 1) fever, with a risk ratio of 1.8; and 2) a combined measure of any mild adverse event, with a risk ratio of 1.7¹.

In an analysis of post-marketing data from VAERS, there were an estimated 0.6 serious events reported per 100,000 doses distributed. Serious adverse events were defined as reports of death, hospitalization, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly². For the ViCPS vaccine, the meta-analysis found that pain and swelling at the injection site were significantly more common among vaccinees than among placebo recipients, with a risk ratio of 8.0 (95% CI 3.7–17.2) for pain and 6.0 (95% CI 1.1–34.2) for swelling at injection site¹. In the VAERS post-marketing study, the ViCPS vaccine was also

associated with a similarly low rate of serious events as the Ty21a vaccine² [¹Anwar et al. Cochrane Database Syst Rev. 2014; ²Begier et al. Clin Infect Dis. 2004].

Contraindications for both Ty21a and ViCPS were hypersensitivity to any component of vaccine^{1,2}. ACIP's general recommendations on immunization suggest that live bacterial vaccines, like Ty21a, are generally contraindicated in pregnant women³. Additionally, the Ty21a vaccine is contraindicated in immunocompromised persons and should not be administered during an acute febrile illness¹ [¹Vivotif Package Insert www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142807.pdf; ²Typhim Vi Package Insert www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf; ³ACIP. General Recommendations on Immunization. 2011].

Because the Ty21a vaccine contains live bacteria, persons should avoid taking antimicrobial agents if possible three days before and after administration of the vaccine¹. However, certain antimalarial prophylaxis medications can be taken at the same time as vaccine², which is relevant, given that many patients are travelers. Also, Ty21a can be co-administered with other live vaccines, including the yellow fever vaccines². The ViCPS vaccine should be given to pregnant women only if clearly needed³ [¹Vivotif Product Monograph. http://www.crucellvaccines.com/canada.com/pdf/vivotif_pm.pdf; ²ACIP. General Recommendations on Immunization. 2011; ³Typhim Vi Package Insert www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf].

Regarding the minor proposed updates to the current ACIP recommendations regarding who should receive vaccine, the first statement pertains to travelers. No substantive changes are proposed for 1994 recommendation for this group. Readers are directed to the current CDC website for the most updated guidance on countries:

“Travelers to areas in which there is a recognized risk of exposure to Salmonella serotype Typhi (see cdc.gov/travel/)

- *“Risk is greatest for travelers to developing countries (e.g., countries in Latin America, Asia, and Africa) who have prolonged exposure to possibly contaminated food and drink, although short-term travelers are also at risk.*
- *“Multidrug-resistant strains of Salmonella serotype Typhi have become common in many regions, and cases of typhoid fever that are treated with drugs to which the organism is resistant can be fatal.*
- *“Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink. Typhoid vaccines are not 100% effective, and vaccine-induced protection can be overwhelmed by large inocula of Salmonella serotype Typhi.”*

The second statement focuses on those with intimate exposure (e.g., household contacts). Changes to the 1994 recommendation for household contacts are for the carrier to be specified as “chronic” and for chronic carriage to be defined as excretion >1 year. The purpose of this change is so that the recommendation is not misconstrued as applying to close contacts of any person with typhoid fever and not just chronic carriers:

“Persons with intimate exposure (e.g., household contact) to a documented Salmonella serotype Typhi chronic carrier (defined as excretion of Salmonella serotype Typhi in urine or stool for >1 year)”

The third statement regards microbiologists and laboratory workers, with a change to the 1994 recommendation of “Microbiology laboratorians who work frequently with *S. typhi*”:

“Microbiologists and laboratory workers who work with cultures of Salmonella serotype Typhi or with specimens that contain this organism or who work in laboratory environments where these cultures or specimens are handled.”

No substantive changes are proposed regarding the choice of vaccine. As in the 1994 statement, no preference is given between the ViCPS and oral Ty21a vaccines. The inactivated whole-cell vaccine that is no longer available has been deleted from the recommendation.

In summary, the current 1994 typhoid vaccine statement is outdated. No substantive changes are proposed to the recommendations are proposed. The updated statement was presented during this session for an ACIP vote. It reflected a change in vaccine availability, with the whole-cell vaccine being removed, new data on typhoid epidemiology, and newer data on vaccine effectiveness and safety.

Discussion Points

Dr. Temte thanked Drs. Mahon and Jackson for a very succinct presentation. He reminded everyone that ACIP strives to review, renew, reaffirm, retire, or revise its statements every 5 years. This statement is now 20 years old. The biggest changes include the elimination of one vaccine and some minor wording. There was some discussion regarding whether this recommendation should be subjected to a formal GRADE review. Given the Ebola situation, there has been a shortage of time within CDC over the last few months. In addition, nothing has really changed from the original recommendation. Systematic reviews have strongly suggested that there is efficacy as previously stated, and the safety profile has not changed.

Dr. Schaffner (NFID) noted that 90% of the cases are travel-associated. Of those, 80% to 85% are among travelers to Bangladesh, India, or Pakistan. He was curious to know who these travelers are, and was thinking analogous to malaria. That is, are these people who were born in the US who are traveling to these countries? Or, are many of them people who were born in these countries, moved to the US, and returned to visit family? This is very important because if it is the latter, perhaps a sentence or two might be included to emphasize that those are also individuals at risk. Similarly, many people do not take malaria chemoprophylaxis when visiting their country of origin.

Dr. Mahon replied that most of the travelers are people who are visiting friends and relatives, but who were not necessarily born in those countries.

Dr. Messonnier pointed out that the attempt to clarify the recommendation for laboratory workers was itself confusing. She wondered whether the intent was to recommend vaccination for laboratory researchers who work with this organism, or local clinical laboratories who may receive specimens from returning travelers. If the intent was local laboratorians, she asked whether the potential number of people who would be impacted had been quantified. The recommendation potentially could include a large number of people.

Dr. Jackson indicated that this was recently revisited. There is a concern that making such a broad recommendation may apply to more people than initially intended. A few cases continue to occur among laboratory and clinical laboratory workers. Perhaps the wording could be revised to include the word “frequently” such that the statement would read “who work frequently with cultures of Salmonella serotype Typhi.”

Dr. Fryhofer (AMA/ACP) asked whether the oral vaccine still needs to be refrigerated. Dr. Jackson replied that it does.

Dr. Pickering pointed out that children are often exposed to people who have traveled to these areas of the world when they return. The returning travelers may be asymptomatic, but the children who are exposed to them may develop typhoid fever.

Dr. Belongia noted that there seem to be relatively few cases coming from Latin America, so he wondered whether the epidemiology had changed and the risk decreased in Latin America.

Dr. Mahon replied that while she did not recall the exact percentages, and she had read that overall the incidence has been decreasing, there are travel-associated cases reported to CDC from travel to Latin America. A number of cases are also seen among travelers from the Caribbean. Therefore, vaccines are still recommended for travelers to those areas.

Dr. Jean Smith was struck by the fact that only 20% of travelers are receiving vaccine. Her daughter went to India and Nepal last summer, so she paid about \$50 for the oral typhoid series at Publix. She wondered whether cost and/or lack of awareness are issues.

Dr. Mahon responded that they do not have this information, but would like to acquire it. She suspects that as Dr. Schaffner pointed out, central to the issue of low vaccination rates is that people do not think about it. When traveling to these countries to visit friends and relatives, it feels like going home. Efforts to reach those groups would be the most effective way of decreasing rates of typhoid in this country. CDC knows whether people are traveling to visit friends and relatives because that is reported as part of the enhanced surveillance for typhoid in this country. She shared an anecdote from a colleague who is of Indian descent with whom she was discussing this session earlier in the week. With a startled look on his face he said, “You know, my father is visiting India right now and it never occurred to me to tell him to get vaccinated.”

Given that the oral vaccine is live attenuated, Dr. Loehr asked whether the same 28-day rule applied as for other live attenuated vaccines. If so, he suggested pointing that out in the recommendation.

Dr. Jackson said he would review this information. As he recalled, the language in the 2011 general recommendations on immunization from ACIP states that there is not a contraindication to administering live vaccines together with typhoid vaccine.

Dr. Loehr clarified that simultaneously is fine, but if one is given, there must be 28 days before another live attenuated vaccine.

Dr. Mahon said that the difference may be because it is administered orally. The biology is different with parenterally-administered live viral vaccines.

Dr. Kroger clarified that with respect to the 28-day rule for non-simultaneous vaccination of live vaccines, the general recommendations apply to injectable and intranasal vaccines but not oral vaccines, so it would not apply in this case.

Ms. Pellegrini was puzzled over the precaution that the vaccine should be given to pregnant women only if “clearly needed.” She was trying to think about cases in which it might be indicated but not “clearly needed.” She wondered if, for example, they were thinking of a pregnant woman going on a cruise with ports of call in these countries.

Dr. Jackson replied that the statement came directly from the current FDA-approved vaccine label, with no changes to that. Further consideration can be given to how this should be interpreted.

Dr. Mahon added that the scenario suggested by Ms. Pellegrini would be the type of situation that would apply. The risk-benefit balance would differ for someone traveling to a location with limited access to clean food and water for a prolonged period of time during pregnancy versus a pregnant woman traveling by cruise ship to ports of call in these countries where they would not have prolonged exposure.

Dr. Decker (Sanofi Pasteur) emphasized that the pregnancy language is regulatory and is prescribed by the Code of Federal Regulations, so it needs to be interpreted with that in mind.

Vote: Typhoid Vaccine Recommendation

Dr. Reingold made a motion to approve the Typhoid Vaccine Recommendation as proposed, including the minor changes suggested during the discussion. Dr. Rubin seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. Two members were absent. The disposition of the vote was as follows:

13 Favored:	Bennett, Belongia, Bocchini, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A
2 Absent:	Campos-Outcalt, Harriman

Vaccine Safety

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

During this session, Dr. Shimabukuro presented an overview of the proposed changes to the VAERS reporting form. As a reminder, VAERS is a national spontaneous reporting system for adverse events after US-licensed vaccines. In recent years, VAERS has received approximately 30,000 US reports annually. VAERS accepts reports from healthcare providers,

manufacturers, and the public. Signs and symptoms of adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms and are entered into the database. VAERS is jointly administered by CDC and FDA, and was authorized by the National Childhood Vaccine Injury Act (NCVIA) of 1986.

Currently, there is a secure online submission process for VAERS. Approximately 30% of reports in recent years have been submitted using this process. Most reports are received as mailed or faxed hardcopies in paper form. In rare instances, reports are made via telephone through a VAERS customer service representative if someone has no other way to submit a report. Reporter types overall include vaccine providers (36%), vaccine manufacturers (34%), patients/parents (15%), and others (15%). There is variability among individual vaccines.

The current VAERS-1 report form is a paper form that has been in use since 1990. It must be downloaded, printed, and completed by hand. Forms are mailed or faxed to the VAERS contractor, and manual processing and data entry procedures are required and are fairly resource-intensive and time-consuming. Hardcopies are scanned and uploaded to the VAERS image database, so there is a traditional research-type database and an image database of the actual report. The online reporting tool has the same fields as VAERS-1 form in a different presentation. The preference is that the online reporting be used to submit forms. The online interface will time out for security reasons after a period of inactivity, so reports cannot be saved. That is, reports must be completed in a single setting.

The objectives for the proposed VAERS 2.0 form are to:

- Create a fillable/savable electronic reporting form
- Update data fields to address current vaccine safety information needs and changes in vaccination practices over time (e.g., pregnancy, types of facilities, race/ethnicity)
- Modernize the appearance and format of the VAERS form
- Modernize reporting procedures (implement electronic document upload capability with the VAERS 2.0 form)
- Ensure data collected on the VAERS 2.0 form allows for comparisons to be made with older data (i.e., historical comparisons between VAERS-1 and VAERS 2.0 data)

There are several reasons for revising the VAERS form. Some fields on the current VAERS form, VAERS-1, have limited public health and/or regulatory value. That was determined by meeting with ISO staff who work with VAERS data on a daily basis, as well as CDC's colleagues at the FDA who use VAERS data for regulatory purposes. Other important information is not being collected. Some fields are no longer relevant due to changes in the immunization program. The language in some fields is confusing and needs clarification. Fields used in paper reporting and for manual processing will no longer be necessary (e.g., manufacturer fields after the transition to the ICH E2B(R3) message standard). New fields, such as pregnancy, are needed because of new recommendations and patterns of vaccine uptake. Handwritten mailed and faxed paper reporting is an inefficient way to conduct vaccine safety surveillance. Paperless reporting using an electronic form would eliminate most manual processing and much data entry, mitigate problems with poor handwriting and non-standard reporting, take advantage of smart features (auto-population, drop down menus, programmed

check boxes, pop-up instructions/reminders, logic checks), allow for standardized data elements (dates and times), and address the complaint of getting timed out on the online reporting tool (i.e., would offer an electronic alternative to using the online reporting tool). Manufacturers are transitioning to fully electronic reporting using the ICH E2B(R3) message standard, so it makes sense to transfer non-manufacturer reporting to electronic reporting.

A number of actions have already occurred in the VAERS 2.0 form development process. Initial internal development, review, and revision have been done by CDC, FDA, and VAERS contractor staff. Review and revision are ongoing. External review has been done by immunization partners (e.g., CDC immunization program, NVPO, HRSA, DoD, ACIP liaison representatives, state immunization program officials, and other partners). Cognitive interviews have been conducted with potential reporters (e.g., physicians, nurses, pharmacist, parents, and patients) and revisions have been made based on the results of those interviews. Cognitive interviews are commonly used to validate questions in surveys. The form has been presented to the federal Immunization Safety Task Force (ISTF). Follow-up interviews have been conducted with a sample of individuals who completed the cognitive interviews to test the revised form. The form has been presented to the ACCV and NVAC. The contractor conducted computer testing of a “smart” form with potential reporters, and revisions have been made based on that testing. The form was presented at the FDA Electronic Postmarket Safety Reporting Updates meeting.

The proposed reporting method would be for the reporter to download the VAERS 2.0 form from the VAERS website. The reporter would complete a VAERS 2.0 form on a computer. The form is a fillable/savable PDF document. The reporter would save the VAERS 2.0 report as an electronic document in a local environment, and would upload the report to the VAERS contractor through the VAERS website. The VAERS contractor would then electronically extract the data from the VAERS 2.0 report into the VAERS database (also reviews, redacts and performs Q&A on data), and would generate an individual report for the VAERS image database. There will still be options for manual reporting such as faxing and mailing, at least in the short-term, until technology and connectivity catch up. A full scale VAERS 2.0 report was included in the members’ binders.

The next steps are to solicit public comments through the *Federal Register*, make final revisions, develop the platform to accept electronic VAERS 2.0 submissions and update the online reporting tool to reflect new data elements, implement the VAERS 2.0 form, and evaluate the completeness and quality of VAERS data (pre-post comparison).

Discussion Points

Dr. Temte asked whether there will be any forced answers on the new form, and whether there would be any verification of the incoming information and the information provided by the contractor.

Dr. Shimabukuro replied that there are no forced answers on the new form. If someone enters an illogical answer, there will be a pop-up reminder cautioning them that the answer may be incorrect or that they may want to reconsider. However, the reporter always has the option to override that or leave anything blank that they wish. If an answer is left blank, there will be reminders, but there is never a hard stop on the form. Currently, the VAERS report intake processing and data entry are done by a contractor. There will be no difference in the process for the current form versus the new form, except that now instead of the paper forms being

mailed or faxed to the contractor, the hope is that most of the forms will be uploaded to the contractor electronically.

Dr. Temte observed that there likely would be less variability with the new form and uploading process.

Dr. Riley expressed gratitude for the inclusion of pregnancy-specific information in the VAERS-2 form. She noted that Box #8 states “If pregnant, yes” but states in parenthesis that pregnancy information goes into Box #18, but then it never comes up again to put the pregnancy information in there. The problem with the form and trying to figure out what to do with the information is that the due date or gestational age are almost never known, so it is not possible to time when a vaccination was given. She thought reporters should be forced to include the due date in Box #8, given that this is a critical element. Otherwise, pregnancy information from this form is useless. The point is to try to draw conclusions about vaccines and pregnancy, and the vaccines that are given in the third trimester do not cause birth defects. The rest of the information about pregnancy can go in Box #18.

Dr. Shimabukuro replied that in previous iterations of the form, there was much more detail on pregnancy. Initially the thought was that including checkboxes or questions for specific information would be helpful, but the cognitive testing challenged a lot of the preliminary assumption. The feedback received about the form in general was to simplify it and have reporters fill in information in the text box. Three of the physicians interviewed were OBGYNs. There are instructions below the question on Box #8. Perhaps they could figure out the most important items and include them at the front of the instructions. Many reasonable suggestions were made about the form, but may not appear due to space considerations or not testing well in the cognitive interviews. However, he thought the concern about estimated due date or gestational age could be addressed.

Dr. Loeher (AAFP) suggested adding to Box #18, “If pregnant, due date.”

Dr. Shimabukuro noted that one problem with putting pregnancy in Box #18 is that it is amazing what people will write about if they are tipped off to write about something. Box #18 previously included much more descriptive language. However, in the cognitive interviews, many physicians suggested saying “Describe the event” and leaving it to reporters to enter information. Based on the research conducted in revising this form, sometimes the more details asked, the more potential problems or unintended consequences created.

Dr. Hayes (ACNM) wholeheartedly and completely supported Dr. Riley’s statement that without an actual estimated date of delivery, the data are absolutely useless.

Dr. Belongia found VAERS-2 to be a nice improvement; however, it still involves filling out a form completely. It is just that this will be done on line instead of in hardcopy. For VAERS-3, he suggested taking advantage of the computer technology that allows for branching points. Not everybody has to see the entire form. They see whatever is relevant for what they are filling out. There could be a different pathway for someone who is pregnant that includes variables that others do not see, because they go down a different pathway.

Dr. Shimabukuro replied that while that may be an option for the online reporting tool, the PDF “smart” form is limited in its smartness.

Jane Zucker (New York City Immunization Program) indicated that New York City has a fairly robust registry, which currently has an adverse event reporting module that takes the information from a reported event. That is, it automatically pulls out the vaccine information (e.g., type of vaccine, lot number, demographics on the child, et cetera) and a VAERS form is generated and faxed. Having the electronic online system will be great, because New York City will transition to electronic submission, again, pulling all of the information from the reported event. She emphasized the importance of remembering that immunization information and program managers are also stakeholders, because they will actually take the information and specifications from the online form and build those into registries to try to improve reporting of adverse events as well as the quality of the data submitted.

Dr. DeStefano commented that data gathering does not stop when the form is received. In particular, pregnancy has been a high priority for the ISO office for a few years. That means that when reports of pregnancy are received, additional detailed information is obtained about the pregnancy (e.g., date of delivery, expected date of conception, delivery, birth outcomes, et cetera).

Human Papillomavirus (HPV) Vaccines

Introduction

Joseph A. Bocchini, Jr, MD
Chair, ACIP HPV Vaccine Working Group

Dr. Bocchini reminded everyone that the HPV Vaccine WG has been preparing for licensure of 9-valent HPV vaccine, with potential licensure anticipated in December 2014. The WG is also continuing to review data on 2-dose schedules. As a reminder, Dr. Markowitz reviewed the available data on 2-dose schedules for both of the licensed vaccines during the June 2014 meeting.

In terms of background, the investigational 9-valent HPV vaccine is an L1 VLP vaccine similar to quadrivalent HPV vaccine. It targets 5 additional high risk types (31, 33, 45, 52, and 58). The BLA was submitted to FDA in December 2013 for females 9 through 26 years of age and males 9 through 15 years of age. The trials submitted were conducted with a 3-dose schedule. The data on males 16 through 26 years of age were not part of the BLA submitted in 2013. However, the data from that study are now available and will be presented to ACIP during this session. The HPV Vaccine WG is reviewing data and considering policy options for presentation to ACIP.

Presentations given to ACIP previously regarding investigational 9-valent HPV vaccine include an overview of investigational 9-valent program in October 2013; burden of cancers and cervical pre-cancers attributed to HPV types in the US and 9-valent HPV vaccine pivotal efficacy and immunobridging trials in February 2014; and 9-valent HPV vaccine concomitant use trials, safety data, revaccination study, and policy questions in June 2014. As noted for the 2-dose schedules, a comprehensive review of the data was presented to ACIP in June 2014 on bivalent and quadrivalent HPV vaccines. There was a discussion of the WHO decision regarding the 2-dose schedules for young girls up to the age of 14. At the same time, it was recognized that there is an intersection between consideration of a 2-dose schedule for HPV2 and HPV 4 vaccines with considerations being made as a result of the potential licensure of the 9-valent

HPV vaccine. No data are available for the 9-valent HPV vaccine in a 2-dose schedule; however, a study is underway that is expected to provide data within about a year comparing immunogenicity of a 3-dose to a 2-dose schedule.

Program Summary and New 9-Valent HPV Vaccine Trial Data

Alain Luxembourg, MD, PhD
Director, Clinical Research
Merck & Company, Inc.

Dr. Luxembourg reminded everyone that 9vHPV vaccine is the investigational 9-valent HPV vaccine and qHPV vaccine is the licensed quadrivalent HPV vaccine, known as Gardasil®.

The epidemiology of 9vHPV has been covered in great detail in terms of the relative contribution of HPV types in 9vHPV vaccine to cervical cancers worldwide. Adding the five additional oncogenic types (HPV 31, 33, 45, 52 and 58) to those already in the licensed vaccine increased the potential to prevent additional disease (from 70% to 90% for cervical cancer from 30% to 80% for CIN2/3, and from 25% to 50% for CIN1). These figures may be slightly different by country because these are worldwide figures, but every country will benefit. Overall, coverage could be 85% to 95% worldwide depending on the type of cancer.

The qHPV vaccine is based on VLP and contains an aluminum-based adjuvant. The 9vHPV vaccine is manufactured the same way, using the same VLP as the qHPV plus five additional VLP types and the same adjuvant. The dosage of antigen and adjuvant has been adjusted to insure comparable immunogenicity to the qHPV vaccine.

As a reminder, the key goals of the 9vHPV vaccine clinical program included the following:

- Demonstrate that 9vHPV provides a similar level of protection as qHPV vaccine against infection/disease due to HPV 6/11/16/18
- Demonstrate that 9vHPV is highly protective against infection/disease due to HPV 31/33/45/52/58
- Prove non-inferior immunogenicity in adolescents versus young women (immunobridging)
- Prove non-inferior immunogenicity in young men versus young women (immunobridging)
- Demonstrate an acceptable safety and tolerability profile

These goals were accomplished with four pivotal studies. The data for three of these pivotal studies were presented to ACIP in February 2014 (the results of the fourth pivotal study, Protocol 003, immunobridging in young men, are presented at this meeting):

- Protocol 001: Efficacy study in young women
- Protocols 002 and 009: Immunobridging studies in adolescents

All efficacy and immunogenicity objectives were met for Protocols 001, 002, and 009. Non-inferiority was demonstrated with respect to the 4 original types in the qHPV vaccine.

Non-inferior immunogenicity with respect to HPV 6, 11, 16, and 18 was demonstrated in young women who received 9vHPV vaccine compared with women who received qHPV vaccine. There were very few cases of HPV 6-, 11-, 16- 18-related disease in subjects followed for three to four years, and there was no statistical difference in terms of incidence rates between the

9vHPV and qHPV vaccine groups. Assessment of the HPV 6/11/16/18 disease endpoints for Protocol 001 showed that the 9vHPV disease numbers were very low compared to the historical placebo for Gardasil. This offers supportive evidence that the two vaccine products protect similarly against disease for the original 4 types.

Approximately 97% protection was documented against HPV 31-, 33-, 45-, 52-, and 58-related disease. For these 5 types, there was high efficacy for all the key efficacy endpoints at 96% to 97%. There was also substantial risk reduction in terms of procedures (e.g., biopsy and definitive therapy).

Non-inferior immunogenicity was demonstrated in boys and girls versus young women. The AE profile was similar to that of the qHPV vaccine, except that there were more injection site AEs that were mostly mild to moderate in intensity. The safety profile was also very similar for the two vaccines, the only difference being higher incidence of injection site AEs for 9vHPV vaccine. These injection site AEs were primarily mild to moderate in intensity.

The following supportive studies have been completed, the results of which were presented to ACIP in June 2014:

- Protocols 005 and 007: Concomitant use studies
- Protocol 006: Study in prior qHPV vaccine recipients
- Integrated summary of safety for Protocols 001, 002, 005, 006, 007, and 009

All immunogenicity objectives were met for supportive studies 005, 006, and 007. These studies showed that 9vHPV vaccine can be administered concomitantly with Menactra[®] (meningococcal vaccine: A, C, Y, W-135), Adacel[®] (Tdap vaccine), and Repevax[®] (Tdap-IPV vaccine, licensed in the EU). 9vHPV vaccine was highly immunogenic in prior qHPV vaccine recipients.

Evaluation of the integrated safety data for all six studies (001, 002, 005, 006, 007, and 009) demonstrated that the 9vHPV vaccine was generally well-tolerated in over 13,000 subjects. The AE profile was generally comparable across age, gender, race, and ethnicity. The AE profile was similar to that of qHPV vaccine. There were more injection-site adverse events with 9vHPV, but these were mostly mild to moderate in intensity. 9vHPV was generally well-tolerated in prior qHPV vaccine recipients.

All of the data previously presented were part of the original FDA filing. Protocol 003 the women-men immunobridging study, was not included in the filing, but was presented at this meeting. The study was designed to include 1100 young women 16 through 26 years of age, 1100 heterosexual men (HM) 16 through 26 years of age, and 300 men having sex with men (MSM) 16 through 26 years of age. Vaccination was administered as a 3-dose regimen (Day 1, Month 2, and Month 6). This was an open label study in which all subjects received 9vHPV vaccine. The key endpoints for immunogenicity were anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers at Day 1 and Month 7. The key endpoints for safety were Vaccination Report Card (VRC)-aided surveillance and SAEs for Day 1 through Month 12.

The key objectives for Protocol 003 were as follows:

Immunogenicity

- ❑ To demonstrate non-inferior immunogenicity of 9vHPV vaccine in men (HM) 16 through 26 years of age versus women 16 through 26 years of age
- ❑ To summarize 9vHPV vaccine immunogenicity in MSM
 - Rationale: Though not fully understood, the immunogenicity of qHPV vaccine was lower in MSM than in heterosexual men (secondary objective; results not included in this presentation in the interest of time)

Safety

- ❑ To evaluate the safety/tolerability of the 9vHPV vaccine in young men and young women 16 through 26 years of age

The study showed that non-inferior immunogenicity was demonstrated in young heterosexual men versus young women for all 9 vaccine HPV types. These data support bridging of efficacy findings in young women 16 through 26 years of age to men 16 through 26 years of age. In terms of safety, the vaccine was generally well-tolerated in young men and young women, with a lower frequency of AEs in young men versus young women. This is similar to the previous safety findings for qHPV vaccine.

In summary, the clinical studies for the 9vHPV vaccine showed that:

- ❑ The immune response for the 9vHPV vaccine was non-inferior response with respect to the original types compared to the qHPV vaccine.
- ❑ Approximately 97% protection was demonstrated against HPV 31, 33, 45, 52, and 58-related disease.
- ❑ Non-inferior immunogenicity was demonstrated in boys and girls versus young women, and in young men versus young women.
- ❑ 9vHPV vaccine was generally well-tolerated, and the AE profile was similar to that of the 4-valent vaccine. There were more injection-site AEs with the 9vHPV vaccine, but most were mild to moderate in intensity. Over 15,000 subjects received 9vHPV vaccine.
- ❑ 9vHPV vaccine can be co-administered with Menactra[®] and Adacel[®]
- ❑ 9vHPV vaccine is generally well-tolerated, and is highly immunogenic in prior qHPV vaccine recipients.

The 9vHPV vaccine is still an investigational product under review by the FDA.

Cost-Effectiveness of 9-Valent HPV Vaccination

Dr. Marc Brisson

**Canadian Research Chair Modeling Infectious Diseases
Associate Professor, Université Laval**

Dr. Brisson's presentation focused on the impact and cost-effectiveness of the 9-valent compared to the 4-valent HPV vaccine in the US. The modeling team that produced these results is from Canada, the UK, and CDC. He thanked the CDC internal peer reviewers for valuable comments to this presentation, and indicated that the model was funded by a variety of sources from Canada, the US, the EU, and the UK.

The study question for the model was, “From the societal perspective, what is the additional impact and cost-effectiveness of the 9-valent compared to 4-valent (quadrivalent) HPV vaccine in the context of an established 4-valent HPV vaccine program in the US?” The objective was to evaluate the additional population-level effectiveness and incremental cost-effectiveness of switching from the 4-valent to the 9-valent HPV vaccine in the US.

To achieve this objective, an individual-based transmission-dynamic model known as HPV-ADVISE was used. This model takes into account the direct effects of vaccination on vaccinees, as well as herd immunity effects. This model was developed to answer policy questions in Canada, but has also been used to assess 2-dose HPV vaccination in the UK and for the WHO. The model included six components: demographics, sexual behavior HPV transmission, natural history of disease, vaccination, cervical screening and treatment, and economics. The population is open and stable, meaning that the number of individuals who enter the population is equal to the number of people who die of natural causes. Age-specific mortality was based on US data. For HPV infections, 18 genotypes were modeled individually, including: 6/11/16/18/31/33/45/52/58. Also modeled were HPV-related diseases, including anogenital warts (AGW); cervical cancer (SCC and adenocarcinoma); and cancers of the anus, oropharynx, penis, vagina, and vulva [Van de Velde et al. JNCI 2012 104(22):1712-23].

The more complex these models become, the more they look like a video game. For them to be really worthwhile for a public health decision, the model has to be calibrated and confronted to actual data to find the appropriate parameters to represent the epidemiology and behavior of a population. An extensive calibration process is used that includes three steps. For all of the parameters in the model, a systematic review of the literature to find the minimum and maximum value of each of the parameters (Step 1). After hundreds of thousands of combinations of these parameters are sampled (Step 2), the parameter sets are put through the model to find those parameter sets that actually fit the US data (Step 3). Fitting is done to a lot of highly stratified data, such as the following:

- Sexual and screening behavior (stratified by gender and age)
- HPV prevalence (stratified by HPV type, gender, age, and sexual activity)
- Incidence of AGW, cervical lesions, cervical cancer and other HPV-related cancers (stratified by HPV type, gender, and age)

In total, the model was fit to 826 data points. The result was 200,000 different combinations of parameters that were sampled from the prior parameter distributions. From these, 50 parameter sets were found that produced a very good fit to the 826 pre-specified data target points. They were then run again through the model with vaccination to get effectiveness. Dr. Brisson showed illustrations of the model fits for sexual behavior model, HPV prevalence in women, screening, and squamous cell carcinoma (SCC).

Once the model fit the situation in the US, the next step was to determine the impact of HPV vaccination. To do this, vaccine efficacy parameters are needed. There were two scenarios for 4-valent efficacy because in a systematic literature review Dr. Brisson’s team conducted, the 4-valent vaccine was found to protect against the types in the vaccines in addition to having some cross-protection to the other types in the clinical trial. Whether this is true cross-protection or how long it will last are unknown, so all of the predictions were done with two scenarios: one with cross-protection and the other without. Obviously, this assumption can have an impact on the additional gains from the 9-valent vaccine. It was assumed that the 9-valent vaccine is as

effective as the 4-valent vaccine against the 4-valent types and that it is 95% effective against the five additional types.

The economic analysis is from the societal perspective. All direct medical costs were included. The primary outcome measure was cost per quality adjusted life years (QALYs) gained. Discounting of 3% was used for costs and benefits over a 70-year time horizon. The cost of the vaccine with administration was assumed to be \$145/dose for the 4-valent vaccine and \$158/dose for the 9-valent vaccine. These numbers were based on a Merck presentation at the 29th International Papillomavirus Conference in 2014 on the cost-effectiveness of the 9-valent vaccine.

In terms of predictions, it is important to model the US program as closely as possible. Therefore, vaccination was introduced in 2007 in females only with the quadrivalent vaccine. In 2011, gender-neutral vaccination with the 4-valent vaccine was added. Now in 2014, decisions can be made either to continue with the 4-valent gender-neutral strategy or to switch the program to a 9-valent scenario. Two scenarios were modeled, one in which the US vaccinates girls only with 9-valent vaccine and maintains 4-valent use for boys or one in which there is a complete switch from the 4-valent gender-neutral vaccination to the 9-valent gender-neutral vaccination.

To model the situation in the US as appropriately as possible, 3-dose vaccine coverage was used from the NIS. Age-specific 3-dose uptake rates were used (e.g., the annual percent of vaccinated individuals with 3 doses among those who had not previously received 3 doses). For 2007 through 2013, observed uptake rates were used. From 2014 on, uptake rates were assumed to be constant at 2013 levels. This means that in 2013 the data were produced for the coverage of 13 through 17 year olds, which was about 39% for girls and about 14% for boys. If vaccine uptake rates remain constant, vaccine coverage increases slightly until 2017 due to age and time cohort effects.

In terms of the potential for additional cancer prevention due to use of 9-valent HPV vaccine, most of the cancers are due to 16/18, which are already targeted by the 4-valent vaccine. However, there are opportunities for additional gains. In assessing cost-effectiveness and the impact of a vaccination program, it is necessary to determine the number of cases per year that could be prevented. The greatest gain from the 9-valent vaccine would be by additional prevention of cervical cancer.

In a scenario of 4-valent vaccination of girls and boys compared to a 9-valent gender-neutral vaccination under the base case assumptions and assuming no cross-protection for the 4-valent, with the 4-valent vaccine there would be substantial reductions in CIN 2/3 to about 61% and cervical cancer to about 65%. By switching to a 9-valent vaccine, there would be an additional 19% reduction in CIN 2/3 and 14% reduction in cervical cancer. In the same scenario but with cross-protection, the additional benefits of the 9-valent are reduced from 19% to 12% for CIN 2/3 and from 14% to 10% for cervical cancer. There are still substantial gains, even if cross-protection is assumed. Another strategy regards moving from a 4-valent gender-neutral strategy to a 9-valent gender-neutral strategy. Most of the benefit of this type of switch would be from vaccination of girls with the 9-valent vaccine.

There are other benefits to the vaccine in addition to CIN 2/3 and cervical cancer, including oropharyngeal cancer and anogenital warts. The additional benefits of the 9-valent are somewhat smaller for these outcomes, which is to be expected. In the model, there was no difference in impact on anogenital warts between the 4-valent and the 9-valent because it was assumed that the 4-valent and 9-valent had the same efficacy for anogenital warts. For oropharyngeal cancer, there was a slight increase in benefits by vaccinating with the 9-valent vaccine. This added benefit is quite similar to the other cancer sites.

There are different ways of looking at the overall impact of vaccination. In terms of the health outcomes prevented over 70 years for the different scenarios modeled, the added benefit of moving from a vaccine program with no cross-protection to a 9-valent girls and boys strategy would be an additional 87,000 cancers prevented over 70 years. This would relate to a number needed to vaccinate (NNV) of 1000, meaning that 1 additional cancer case would be prevented for every 1000 individuals switched from the 4-valent to the 9-valent vaccine. The model also predicts that an additional 26,000 cancer deaths would be prevented by switching to the 9-valent vaccine. The additional benefits of the 9-valent vaccine are lower when cross-protection is assumed for the 4-valent vaccine. When cross-protection is assumed for the 4-valent, the NNV increases and the additional number of cases prevented by the 9-valent vaccine is reduced, so the model predicts 47,000 cancer cases prevented and 14,000 deaths prevented. The added benefit in switching from 9-valent in girls and 4-valent in boys to 9-valent in girls and boys is quite small.

In terms of cost-effectiveness, the primary outcome for benefit is QALYs gained. The primary benefit of QALYs gained of vaccinating with the 4-valent vaccine is prevention of cervical cancer and other HPV-related cancers. The incremental benefits of switching girls to 9-valent vaccine and continuing to vaccinate boys with 4-valent vaccine are smaller, but that is understandable. The primary benefit in this scenario is in the prevention of cervical cancer. The incremental benefits of switching from a strategy of 9-valent in girls and 4-valent boys to 9-valent girls and boys is small. Regarding incremental healthcare costs saved from vaccination, the primary savings using a 4-valent vaccine strategy is in costs related to cervical screening. Comparing 9-valent vaccine in girls and 4-valent boys to 4-valent girls and boys, the main primary saving is due to costs related to cervical screening. There are very few gains in averted healthcare costs when switching from a strategy of 9-valent in girls and 4-valent boys to 9-valent girls and boys.

Regarding cost-effectiveness assuming no cross-protection for the 4-valent vaccine, the 4-valent vaccine compared to no vaccination is estimated to be highly cost-effective at \$6,400 per QALY gained. A scenario with 9-valent vaccine for girls and 4-valent vaccine for boys is cost-saving. Switching to a 9-valent program would be cost-saving, and the majority of these cost savings would be in the prevention of the costs related to cervical screening. The incremental costs are quite low in a gender-neutral 9-valent scenario (compared to a scenario with 9-valent vaccine for girls and 4-valent vaccine for boys), though the cost-effectiveness ratio is still about \$31,000 per QALY. However, there is a lot of uncertainty around that cost-effectiveness ratio, which goes from very cost-effective to not cost-effective at all. Whereas there is considerable uncertainty in the cost-effectiveness of a 9-valent gender-neutral strategy compared to a strategy of 9-valent vaccine for girls and 4-valent vaccine for boys, there is much less uncertainty in the cost-effectiveness of a 9-valent gender-neutral strategy compared to a 4-valent gender-neutral strategy. When using a 4-valent gender-neutral strategy as the comparator, the cost-effectiveness of a 9-valent gender-neutral strategy is not particularly sensitive to assumptions about cross-protection of the 4-valent vaccine.

In order to determine how robust these results were to changes in key parameters, sensitivity analyses were performed varying certain parameters to assess their impact. The model and predictions were very robust to the sensitivity analyses. Varying the duration of efficacy did not make a major difference on the results. Vaccine coverage was changed to higher coverage, and a scenario was assessed in which a high proportion of 13-year old girls and boys would be vaccinated at 13 instead of the older ages. Also assessed was a scenario with minimum cost to the healthcare system, meaning that costs related to screening would be very low. Even in that scenario, the switch to the 9-valent vaccine was cost-saving. In the base case, primary cervical cancer screening was modeled as cytology-based screening. To determine what might happen with changes to screening guidelines, an alternate scenario was modeled in which HPV co-testing was incorporated into cervical cancer screening. Even with HPV co-testing in women 30 through 65 years of age, the switch to the 9-valent vaccine was cost-saving. Even when assuming cross-protection of the 4-valent vaccine, the results for the 9-valent vaccine were very insensitive to changes in key parameter values. One parameter that is very important is the cost of the intervention. The base-case assumption was that the cost difference between the 9-valent and 4-valent vaccine was \$13 per dose. At a difference of \$13 per dose and when assuming no cross-protection of the 4-valent vaccine, 9-valent vaccine was cost-saving in all of the scenarios. In the cross-protection scenario, 9-valent vaccine was cost-saving in most of the scenarios examined. However, as the additional cost per dose increases beyond \$13, the cost per QALY gained by 9-valent vaccine increases.

In all modeling and cost-effectiveness exercises, there are many limitations. Dr. Brisson pointed out three main limitations. The first is that duration of 4-valent and 9-valent vaccine efficacy and future vaccination coverage in the US remains unknown. However, duration of protection and vaccination coverage were varied and these parameters had no real impact on the conclusions. Cytology-based screening and HPV co-testing were also modeled, but screening may change in the coming years. For example, primary HPV testing might be considered. If the changes to screening result in less costly and/or more effective cervical cancer prevention, the incremental cost-effectiveness of the 9-valent vaccine may become less favorable. The cost-effectiveness of the 9-valent versus the 2-valent vaccine was not presented because that is not the strategy being used in the US. However, the HPV-ADVISE model suggested that in Canada, the 2-valent vaccine was less cost-effective than the 9-valent and 4-valent scenarios.

In summary of population-level effectiveness predictions, the current US 4-valent girls and boys strategy is expected to reduce HPV-related diseases substantially. A 61% reduction in CIN2/3 and 65% reduction in cervical cancer are anticipated after 70 years, assuming that there is no cross-protection. One HPV-related cancer would be prevented for every 250 vaccinated individuals. Switching to a 9-valent girls and boys strategy is expected to further reduce pre-cancerous lesions and cervical cancer, with relatively less additional impact on other HPV-related outcomes. A 19% additional reduction in CIN2/3 and 14% additional reduction in cervical cancer are anticipated after 70 years, assuming no cross-protection of the 4-valent. One additional HPV-related cancer would be prevented for every 1000 vaccinated individuals with the 9-valent instead of the 4-valent vaccine. Vaccinating girls with the 9-valent vaccine provides the great majority of benefits of a 9-valent girls and boys program.

To summarize cost-effectiveness predictions, the current US 4-valent girls and boys HPV vaccination program is highly cost-effective. Switching to a 9-valent girls and boys program is likely to be cost-effective and cost-saving. Vaccinating girls with the 9-valent vaccine provides the majority of cost savings and QALYs gained of a 9-valent girls and boys program. The results are robust across a range of plausible assumptions, including cross-protection or no

cross-protection of the 4-valent vaccine, price, duration of protection, health care costs, and burden of illness.

Discussion Points

Dr. Orenstein (NVAC) noted that one question that will likely arise in policy-making deals with what to do with persons who are already fully vaccinated against the 4 types. He wondered whether the cost-effectiveness of vaccinating these individuals with 9-valent had been modeled.

Dr. Brisson responded that the cost-effectiveness of revaccinating 13 through 17 years old females who have already received 3 doses of the 4-valent vaccine was assessed in exploratory analyses. The incremental cost-effectiveness ratio was \$88,000. The range was from \$52,000 to \$300,000 so there was a lot of variability in this. It is important to note that simplifying assumptions were made that biased the results in favor of revaccination and that in reality the cost-effectiveness of revaccination would likely be less favorable. Revaccinating older women or revaccinating boys would be even less cost-effective than revaccinating females 13 to 17 years old.

Dr. Temte asked whether that would be administering 3 additional doses of 9-valent for those who already received 3 doses of 4-valent.

Dr. Brisson confirmed that the assumption was 3 doses of 9-valent vaccine given to those who already received 3 doses of 4-valent.

Referring to the cost-effectiveness table, Dr. Loehr (AAFP) said he was unclear what was meant by the 1 versus 0 and 3 versus 2 columns.

Dr. Brisson clarified that it was to explain what the comparator was.

Thomas Weiss (Merck) emphasized that the Merck model mentioned earlier that was presented at a recent HPV Congress and to the ACIP WG showed similar results and reached similar conclusions.

Dr. Temte asked how likely the price used in the modeling is to be what is observed in the future.

Thomas Weiss (Merck) indicated that this has not yet been determined, but will be announced at the time of licensure.

Dr. Schuchat indicated that the price announced at licensure may not be the price over time. The VSD prices are posted on CDC's website, which are updated when the price changes. The price has not been stable since the original licensure.

Dr. Belongia asked whether the prices generally go down afterward.

Dr. Schuchat replied that the price has increased annually.

Dr. Sun (FDA) asked whether the modeling took into account the potential indirect effects or herd immunity.

Dr. Brisson responded that this model did take herd protection into account. The model takes into account all partnership formation and separation. Sexual behavior, transmission of HPV, and the indirect effects of preventing someone from being infected are modeled. If a woman is prevented from having HPV, she is also not transmitting the HPV to her male partner or partners.

Dr. Kinsinger (DVA) asked whether the drop in screening costs referred to the initial screening, or if Dr. Brisson was suggesting that the costs were lower due to less abnormal lesions that need to be followed.

Dr. Brisson replied that the screening costs being saved would be primarily due to less cost to follow-up and management of abnormal lesions.

Dr. Reingold wondered how practical having different vaccines for girls and boys would be for practitioners in terms of storage, confusion, et cetera.

Dr. Temte inquired as to whether Merck would continue to make both vaccines, or if it would be akin to the move from PCV7 to PCV13.

Julie McCafferty (Merck) indicated that Merck anticipates that there will be demand for both products in the US, and intends to supply both products until there is a time when the indications for Gardasil[®] and the 9-valent vaccine match. Time would then be allowed for series completion. Merck will also still manufacture 4-valent for outside the US.

Dr. Markowitz suggested that this be further discussed during the Policy Options presentation and discussion.

GRADE for 9-Valent HPV Vaccine

Emiko Petrosky, MD, MPH

EIS Officer

Epidemiology and Statistics Branch

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Centers for Disease Control and Prevention

Dr. Petrosky reported that the HPV WG used GRADE to review data related to the 9-valent HPV vaccine. As a reminder, the 9 steps of GRADE are to:

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

The previous presentations included an assessment of the population benefit and a review of the health economic data for the 9-valent vaccine. Dr. Petrosky's presentation covered the first 4 steps in GRADE. The remaining steps will be completed and presented during the next ACIP meeting in February 2015.

The first step in GRADE is to develop the policy questions. The questions Dr. Petrosky addressed during this session included:

- Should the 9-valent vaccine be recommended routinely for 11 through 12 year olds?
- Should the 9-valent vaccine be recommended for females aged 13 through 26 years and males aged 13 through 21 years who have not been previously vaccinated?

The next step in GRADE is to consider critical outcomes. The following table shows the outcomes the WG identified and ranked, and whether they were included in the evidence profile for GRADE. The benefits are listed separately for females and males, and the harms are listed jointly:

HPV9 outcome measure ranking and inclusion		
Benefits	Importance	Include in evidence profile
Females		
Cervical precancer ^a	Critical	Yes
Cervical cancer	Critical	Yes
Definitive therapies ^b (cervical)	Critical	No ^c
Oropharyngeal cancer	Critical	No ^d
Vaginal/vulvar cancer	Critical	No
Anal cancer	Critical	No
Anogenital warts	Important	Yes
Males		
Anal cancer	Critical	Yes
Oropharyngeal cancer	Critical	No ^d
Anogenital warts	Important	Yes
Harms (both females and males)		
Serious adverse events	Critical	Yes
Anaphylaxis	Critical	Yes

^aCervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (AIS) 2/3
^bIncludes non-ablative procedures, loop electrosurgical excision procedure, conization
^cRepresented by cervical precancer and cervical cancer
^dNo data available on outcomes

In red are the outcomes not included in the evidence profile. Definitive therapies were not included since they are represented by cervical pre-cancer and cervical cancer, or oropharyngeal cancer as there are no data for this outcome from any HPV vaccine study. For simplicity, vaginal/vulvar cancer and anal cancer were not included in the evidence profile for females, instead focusing on the most prevalent outcomes in women: cervical pre-cancer, cervical cancer, and anogenital warts. For males, anal cancer and anogenital warts were assessed. For harms in both females and males, SAEs and anaphylaxis were assessed.

The next step in GRADE is to review and summarize the evidence of benefits and harms, which were performed after reviewing published and unpublished data relevant for the 9-valent vaccine. Before presenting the data, Dr. Petrosky mentioned a few considerations. Both the 9-valent and quadrivalent vaccines are recombinant HPV virus-like particle (VLP) vaccines with the same manufacturing process, and both contain HPV 6/11/16/18 VLPs, the 4 original types. The 9-valent vaccine contains 5 additional VLPs. The 9-valent vaccine program compared the 9-valent vaccine to the quadrivalent vaccine as the active comparator. However, because the quadrivalent vaccine has high efficacy, there were few disease endpoints due to the 4 original types in the comparator cohort, and the efficacy of the 9-valent vaccine for the 4 original types could not be directly assessed. Instead, the 9-valent vaccine was immunobridged to the

quadrivalent vaccine to demonstrate non-inferior immunogenicity and comparable efficacy. Because of this, data from the quadrivalent vaccine trials were considered for the 4 original types for GRADE of the 9-valent vaccine. Of note, neutralizing antibody is considered to be the mechanism of protection for HPV vaccination. Vaccines induce high antibody titers; however, no minimum level of protective antibody has been identified.

The following table shows the quadrivalent phase 2 and 3 efficacy RCTs submitted for quadrivalent vaccine licensure that were considered for GRADE of the 9-valent vaccine for the 4 original types. In females, there were 3 RCTs and in males 1 RCT comparing the quadrivalent vaccine to placebo:

Per Protocol Population	Protocol	Outcomes
Females aged 16–26 years	007, 013, 015	CIN 2/3 or AIS Anogenital warts
Males aged 16–26 years	020	AIN 2/3 Anogenital warts

As mentioned earlier, the 9-valent vaccine was immunobridged to the quadrivalent vaccine. All of the data examined for GRADE involved the per protocol population from these studies. Of note, although the age groups in these studies do not completely correspond to the age groups in the policy questions, they do closely overlap. Protocol 001 is the pivotal efficacy study that compared the quadrivalent vaccine to the 9-valent vaccine in females aged 16 through 26 years. Protocol 002 compared the 9-valent vaccine in females aged 16 through 26 years to females and males aged 9 through 15 years. Protocol 003 compared the 9-valent vaccine in females aged 16 through 26 years to males of the same age group. Protocol 009 compared the quadrivalent vaccine to the 9-valent vaccine in females aged 9 through 15 years. Protocol 005 and 007, the concomitant use studies, provided additional supportive evidence of 9-valent vaccine immunogenicity and safety.

Dr. Petrosky reviewed and summarized the evidence of benefits, first focusing on the population of females aged 13 through 26 years. The intervention is the 9-valent vaccine and the comparison group is the quadrivalent vaccine. The outcomes were examined by vaccine type, the 4 original types and the 5 additional types. She presented the evidence in older females first, as vaccine efficacy can only be demonstrated in older age groups. Efficacy findings are then immunobridged to the younger age groups. The quadrivalent vaccine trials showed high efficacy. In females, the vaccine demonstrated greater than 98% efficacy in preventing CIN 2/3 or AIS due to the 4 original types and greater than 98% efficacy for anogenital warts.

Regarding data from the study immunobridging the quadrivalent vaccine to the 9-valent vaccine in females, (Protocol 001) for outcomes due to the 4 original types, the 9-valent vaccine demonstrated comparable efficacy in preventing cervical pre-cancer and anogenital warts. For the 5 additional types, the 9-valent vaccine demonstrated greater than 96% efficacy in preventing cervical pre-cancer. The absolute risk difference was 4 fewer cases per 1000 and the number needed to vaccinate (NNV) was 250. Based on the dynamic model of HPV vaccination shown previously by Dr. Brisson, 1 case of CIN 2/3 due to the 5 additional types is prevented for every 51 to 76 females vaccinated with the 9-valent vaccine instead of the

quadrivalent vaccine over a period of 70 years. Protocol 001 found greater than 99% seroconversion after vaccination with the 9-valent vaccine. There was no difference for the 4 original types compared to the quadrivalent vaccine. For the 4 original types, the 9-valent vaccine induced non-inferior GMTs compared with the quadrivalent vaccine. For the 5 additional types, GMTs were superior compared with the quadrivalent vaccine.

The next step in GRADE is to evaluate the quality of evidence. As a reminder, the evidence type ranking used for GRADE is as follows:

1. Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2. RCTs with important limitations, or exceptionally strong evidence from observational studies
3. Observational studies, or RCTs with notable limitations
4. Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

For GRADE of the 9-valent vaccine, all of the evidence types begin with 1 based on starting with either the RCT of the quadrivalent vaccine or the RCT of the 9-valent vaccine.

The evidence type for the benefits due to the 4 original types in older females are shown in the following table:

GRADE for HPV9 in females						
Evidence type for HPV 6/11/16/18-related benefits						
Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Cervical precancer	HPV4 RCT (3) ^a	No serious	No serious	Serious ^c	No serious	2
Supportive data	HPV9 RCT (1), Obs (2) ^b					
Cervical cancer	HPV4 RCT (3) ^a	No serious	No serious	Serious ^{c,d}	No serious	3
Supportive data	HPV9 RCT (1), Obs (2) ^b					
Anogenital warts	HPV4 RCT (3) ^a	No serious	No serious	Serious ^c	No serious	2
Supportive data	HPV9 RCT (1), Obs (2) ^b					

^aData from HPV4 Protocols 007 (RCT), 013 (RCT), 015 (RCT)
^bSupportive HPV9 Protocols 001 (RCT), 002 (Obs), 003 (Obs)
^cDowngrade by 1 for indirectness due to use of immunobridging to HPV4
^dDowngrade by 1 for indirectness due to use of cervical precancer as surrogate marker for cervical cancer

Because the 9-valent vaccine was immunobridged to the quadrivalent vaccine for the 4 original types, the quadrivalent vaccine trials data were graded and data from the 9-valent studies were considered as supportive evidence. The quadrivalent vaccine trials were RCTs without notable limitations, so each outcome began with an evidence type of 1. Starting with cervical precancer, the evidence was downgraded by 1 for indirectness due to the use of immunobridging to the quadrivalent vaccine, resulting in an evidence type of 2. For cervical cancer, the evidence was downgraded again for indirectness due to the use of cervical pre-cancer as a surrogate marker for cervical cancer, resulting in an evidence type of 3. For anogenital warts, the evidence was downgraded by 1 for indirectness, again for the use of immunobridging data, resulting in an evidence type of 2.

For the 5 additional types, Protocol 001, the RCT that compared the 9-valent vaccine to the quadrivalent vaccine in older females was graded as this study was able to demonstrate 9-valent vaccine efficacy for the 5 additional types. For cervical pre-cancer, there was no downgrade for any of the criteria, which kept the evidence type at 1. For cervical cancer, there was a downgrade of 1 for indirectness due to the use of cervical pre-cancer as a surrogate marker for cervical cancer, resulting in an evidence type of 2. This is shown in the following table:

GRADE for HPV9 in females						
Evidence type for HPV 31/33/45/52/58-related benefits						
Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Cervical precancer	HPV9 RCT (1) ^a	No serious	No serious	No serious	No serious	1
Supportive data	HPV9 Obs (2) ^b					
Cervical cancer	HPV9 RCT (1) ^a	No serious	No serious	Serious ^c	No serious	2
Supportive data	HPV9 Obs (2) ^b					

^aData from HPV9 Protocol 001 (RCT)
^bSupportive HPV9 Protocols 002 (Obs), 003 (Obs)
^cDowngrade by 1 for indirectness due to use of cervical precancer as surrogate marker for cervical cancer

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Dr. Petrosky then discussed the younger population, females aged 11 through 12 years. Similar to older females, the outcomes were examined separately for the 4 original types and for the 5 additional types. In the interest of time, for this and the remaining populations, Dr. Petrosky did not present the data for the benefits as these were previously presented to ACIP. She instead focused on the process used to GRADE the evidence and explain the approach for evidence type ranking.

Protocols 002 and 009 were the supportive studies considered for GRADE for the 9-valent vaccine in younger females. Protocol 002 was an immunobridging study that showed the 9-valent vaccine induced non-inferior seroconversion and higher GMTs in younger females, which supports the bridging of efficacy findings in older females to younger females. Protocol 009 showed that the 9-valent vaccine induced non-inferior seroconversion and GMTs compared with the quadrivalent vaccine in younger females, which supports the bridging of efficacy findings from the quadrivalent vaccine to the 9-valent vaccine. For the younger females, the WG started with the evidence type for the older females and did not downgrade for any of the criteria, keeping the evidence type the same. This is because of the high seroconversion rates and higher GMTs in the younger females compared to the older females, and because the efficacy data were from the per protocol population.

Dr. Petrosky next summarized the evidence for the 9-valent vaccine in males, first in the population of males aged 13 through 21 years. Only the outcomes due to the 4 original types were assessed because of the low burden of disease due to the 5 additional types in males. In protocol 020, the quadrivalent vaccine efficacy trial in males, the quadrivalent vaccine demonstrated greater than 74% efficacy for prevention of AIN 2/3 and greater than 89% efficacy for prevention of anogenital warts. For the studies considered for GRADE for the 9-valent vaccine in older males, the WG started with the quadrivalent vaccine trial in males and

considered the data from the 9-valent trial, protocol 003, as supportive evidence. Of note, GRADE for the quadrivalent vaccine in males was presented to the ACIP in 2011. Based on protocol 020, efficacy for prevention of anal cancer had been ranked an evidence type of 2 and anogenital warts an evidence type of 1. There is no study in older males immunobridging the 9-valent vaccine to the quadrivalent vaccine. Instead, there is Protocol 003, which immunobridged the 9-valent vaccine in older females to older males. The 9-valent vaccine induced non-inferior seroconversion and GMTs in older males, which supports the immunobridging of outcome findings in older females to older males.

The following table shows the evidence type for the benefits of the 9-valent vaccine in older males:

GRADE for HPV9 in males						
Evidence type for HPV 6/11/16/18-related benefits						
Benefits	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
Anal cancer	HPV4 RCT (1) ^a	No serious	No serious	Serious ^{c,d}	No serious	3
Supportive data	HPV9 RCT (1), Obs (1) ^b					
Anogenital warts	HPV4 RCT (1) ^a	No serious	No serious	Serious ^c	No serious	2
Supportive data	HPV9 RCT (1), Obs (1) ^b					

^aData from HPV4 Protocol 020 (RCT)
^bSupportive HPV9 Protocols 001 (RCT), 003 (Obs)
^cDowngrade by 1 for indirectness due to use of immunobridging to females of the same age group
^dDowngrade by 1 for indirectness due to use of AIN 2/3 as surrogate marker for anal cancer

Starting with the evidence type of 2 for anal cancer and 1 for anogenital warts, both outcomes were downgraded for indirectness due the use of immunobridging data, resulting in an evidence type of 3 for anal cancer and 2 for anogenital warts.

Focusing on the population of males aged 11 through 12, similarly to older males, the WG only assessed the outcomes due to the 4 original types. One of the supportive studies was Protocol 002, which immunobridged the 9-valent vaccine in older females to younger males. The 9-valent vaccine induced non-inferior seroconversion and higher GMTs in younger males, which supports the bridging of efficacy findings from older females to younger males. In addition, the WG compared the GMTs in younger males from this study with GMTs from older males in Protocol 003. The younger males had higher GMTs compared with the older males, which supports immunobridging from older males to younger males. Thus, for the younger males, the WG started with the evidence type for the older males and did not downgrade for any criteria, keeping the evidence type the same. This is because the younger males had high seroconversion rates and higher GMTs than the older males, and because the efficacy data was from the per protocol population.

Switching to harms, the outcomes under consideration were SAEs, which were examined as days 1 through 15 after vaccination and any time during the study period, and anaphylaxis, day 1 through 15, after vaccination. The harms were examined by older and younger age groups. First focusing on harms in older females and males, 1 RCT (Protocol 001) and 2 observational studies (Protocols 002 and 003) assessed harms in the older age group. The adverse events were similar for the 9-valent vaccine and the quadrivalent vaccine. There were few cases of

vaccine-related SAEs in either group, and only 1 case of anaphylaxis with the 9-valent vaccine, which was determined to be due to a non-study medication. In terms of the evidence type for the harms due to the 9-valent vaccine in older females and males, the WG started with an evidence type of 1 due to inclusion of an RCT. For both SAE and anaphylaxis, only imprecision was downgraded due to the small sample size, resulting in a final evidence type of 2.

For the younger age group, 1 RCT (Protocol 009) and 3 observational studies (Protocols 002, 005, and 007) assessed harms. Once again, the adverse events were similar for the 9-valent vaccine and the quadrivalent vaccine. There were few cases of vaccine-related SAEs in the 9-valent vaccine group and, for the younger age groups, no cases of anaphylaxis in either group. The evidence types for harms of the 9-valent vaccine in younger females and males were similar to the older age groups. The initial evidence type was 1 due to inclusion of an RCT, and for both SAE and anaphylaxis, only imprecision was downgraded due to the small sample size, resulting in a final evidence type of 2.

Dr. Petrosky then summarized the findings and the overall quality of evidence for the 9-valent vaccine by the populations just presented, beginning with the older females. The quadrivalent vaccine trials showed high efficacy for the quadrivalent vaccine, and the 9-valent vaccine demonstrated non-inferior immunogenicity and comparable risk for the outcomes due to the 4 original types. For the 5 additional types, the WG graded the RCT comparing the 9-valent vaccine to the quadrivalent vaccine, which showed a decreased risk for the outcomes due to the 5 additional types. For harms, there were few SAEs and no vaccine-related anaphylaxis. Taking into consideration the evidence types for all 9 types combined and the supportive 9-valent vaccine studies, the overall evidence for benefits and harms in older females was given a final ranking of 2. In younger females, the 9-valent vaccine demonstrated non-inferior immunogenicity, and the evidence types were the same as for older females. For harms, there were no SAEs and no cases of anaphylaxis.

In older males, the quadrivalent vaccine trial showed high efficacy for the quadrivalent vaccine, and the 9-valent vaccine demonstrated non-inferior immunogenicity for the 4 original types. The harms were the same as for the older females. For older males, because there is no immunobridging study comparing the quadrivalent vaccine to the 9-valent vaccine in males, the overall evidence type for the benefits and harms was given a ranking of 3. In younger males, the 9-valent vaccine demonstrated non-inferior immunogenicity, and the evidence types were the same as for older males. The harms were the same as for the younger females.

In conclusion, the overall evidence type for older and younger females was 2, indicating moderate confidence. For the older and younger males, the evidence type was 3, or of low confidence.

Discussion Points

In terms of the indirectness of the data from CIN to cervical cancer, Dr. Gorman (NIH) asked whether there were natural history studies that could provide the percentage of those with CIN who progress and those who resolve spontaneously that could eliminate the downgrading factor. The natural history studies were in the late 1990s and led to the recommendations for the present therapeutic interventions for those. The decision was made that treatment is needed for those because of the percentage that progressed and regressed.

Dr. Markowitz added that they were being very conservative in counting those as indirectness. Downgrading was not done for prevention of the pre-cancerous lesions themselves. They have been very conservative in considering pre-cancer a surrogate for cancer. That is generally what has been considered by regulatory agencies and worldwide.

Policy Options and Discussion

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Dr. Markowitz reviewed the issues and considerations for HPV vaccine recommendation options that have been discussed by the HPV vaccine WG. Policy decisions over the next year will be impacted by the expected licensure of the 9-valent HPV vaccine and the status of data available on 2-dose schedules. For both of these issues, consideration will have to be given to the evidence base, programmatic considerations, and regulatory issues. Dr. Markowitz began with an overview of the current data on vaccine coverage in the US, provided a brief overview of data presented to ACIP at the June 2014 meeting regarding 2-dose schedules, and discussed recommendation considerations and options discussed by the ACIP WG.

Based on the latest National Immunization Survey-Teen (NIS-Teen) national vaccination coverage levels among adolescents aged 13 through 17 years from 2006 through 2012, Tdap and MCV4 coverage increased to approximately 80%. In contrast, while HPV coverage increased initially somewhat in parallel with those vaccines, coverage has plateaued for at least 1-dose and 3-dose coverage. There was an increase between 2012 and 2013, but this was small. At least 1-dose coverage was 57% in 2013 and 3-dose coverage was 38%. Coverage in boys increased after 2011 when the recommendation was made for routine vaccination. Overall, about 70% of those who start the series complete all three doses. Based on estimates of at least 1-, at least 2-, and at least 3-dose coverage in the US, the drop-off between 1 and 2 and 2 and 3 is similar. At 3-dose coverage was 57%, at least 2 dose coverage was 47% in 2013, and at least 3-dose coverage was 38% [MMWR 2014:63;625-33].

There are ongoing efforts to try to increase coverage in the US, including materials to assist providers. There has also been special funding awarded to many project areas to assess communication, education, elimination, and missed opportunities. In addition, there have been partnerships with other organizations.

Since NIS data for 2014 will not be available until sometime next year, to get an idea of what is happening in 2014, cumulative doses distributed in the US were assessed for 2012, 2013, and 2014. Of note, the number of doses administered is not known. This is just to show distributed doses. There was an increase between 2012 and 2013, mirroring the 3.5% increase observed in NIS-Teen between those years. Through August 2014, doses distributed in 2014 were similar to 2013.

Earlier in this session, there was a review of 9-valent HPV vaccine data and GRADE. A review of information on 2-dose schedules was presented to ACIP during the June 2014 meeting. This included data from trials on 2-dose schedules, regulatory approvals and recommendations, countries using 2-dose schedules, and considerations for the US.

Most of the data on 2-dose schedules are from immunogenicity studies. These studies have shown very high seroconversion rates with 2 doses, and GMTs that are non-inferior after 2 doses given at 0 and 6 months in females 9 through 14 years of age compared to 3 doses in females 16 through 26 years of age who received the traditional 3-dose schedule. There are also data from a post-hoc analysis of a 3-dose RCT of the bivalent vaccine that found high efficacy for 2 doses. There are a variety of data from post-licensure effectiveness studies. In general, these found lower effectiveness for 2 versus 3 doses for a variety of outcomes. However, these studies have many limitations, one of which is that the 2-dose recipients did not receive a 0, 6 months schedule. They were persons who were supposed to receive a 3-dose schedule but did not complete it. Second, there could have been confounding in these studies due to differences between the 2-dose and 3-dose recipients.

The following table shows immunogenicity studies of bivalent and quadrivalent vaccine comparing 2 and 3 doses. The top 3 are bivalent vaccine trials and the bottom 2 are quadrivalent vaccine trials. To date there are two published studies for bivalent vaccine and 1 of quadrivalent:

Immunogenicity studies comparing 2 and 3 doses of HPV vaccine						
Study	Country	Vaccine	Design Age and doses	Schedules	Longest followup	
Romanowski Hum Vaccin 2011* Hum Vaccin 2014	Canada/ Germany	HPV2	9-14 2 doses	0, 6	24 mos	
			9-14 3 doses	0, 1, 6	48 mos	
			15-25 3 doses	0, 1, 6		
Puthanakit EUROGIN 2013 ESPID 2014	Multi- national	HPV2	9-14 2 doses	0, 6	~12 mos	
			9-14 2 doses	0, 12		
			15-25 3 doses	0, 1, 6		
Lazcano-Ponce Vaccine 2014	Mexico	HPV2	9-10 2 doses	0, 6	21 mos	
			9-10 3 doses	0, 1, 6		
			18-24 3 doses	0, 1, 6		
Dobson JAMA 2013	Canada	HPV4	9-13 2 doses	0, 6	36 mos	
			9-13 3 doses	0, 2, 6		
			16-26 3 doses	0, 2, 6		
Sankaranarayanan EUROGIN 2013	India	HPV4	10-18 2 doses	0, 6	18 mos	
			10-18 3 doses	0, 2, 6		

*dose ranging study; included other groups as well

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The Romanowski and Puthanakit studies were included in the licensure submissions that GSK submitted for the bivalent vaccine. The Dobson study was included in the submission for the quadrivalent vaccine in some countries. Because the US is primarily using the quadrivalent vaccine, Dr. Markowitz further described the Dobson study. The Dobson study was a 2- versus 3-dose immunogenicity trial. One experimental group received 2 doses at 0 and 6 months and 9 to 13 years. Two comparison groups received 3 doses, one group of 9 through 13 year old girls and one group of 16 through 26 year old women. The primary analysis was a comparison of the 2-dose 9 through 13 year old group with the 3-dose 16 through 26 year old group. In this comparison, non-inferior criteria were met and the antibody response was higher in the 2-dose 9 through 13 year old group. In the analysis comparing the 2-dose and 3-dose schedules in the 9 through 13 year old group, non-inferiority was lost for HPV 18 by 24 months and for HPV 6 by 36 months.

HPV2 and HPV4 have regulatory approval for use as 2-dose schedules from the European Medicines Agency (EMA) and a variety of countries. WHO changed the recommendations in 2014. A 2-dose HPV vaccination schedule is recommended if vaccination is initiated before 15 years. The minimal interval between doses is 6 months. A 3-dose schedule remained

recommended if vaccination initiated on or after 15 years. A 3-dose schedule (0, 1-2, 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected. Several countries recommended 2-dose schedules before the WHO recommendation and regulatory approvals, and more are changing to 2-dose schedules.

In the US, there have been no submissions to FDA for 2-dose schedules. There are no plans for submissions to FDA for the bivalent or quadrivalent vaccines. For the 9-valent vaccine, there are no data on 2-dose schedules in the BLA currently under consideration by FDA. A trial comparing 2-dose and 3-dose schedules has been initiated by the manufacturer. This trial started in December 2013 and the last patient is scheduled to complete the study in July 2015. There are 5 study arms, with 3 experimental 2-dose schedule arms in 9 through 14 year olds. Two comparison groups are receiving a 3-dose schedule in the standard 0,2,6 month schedule. One of the comparison groups includes 9 through 14 year olds, and the other includes 16 through 26 year olds [Clinicaltrials.gov identifier NCT01984697].

Given the expected licensure of 9-valent HPV vaccine and the status of data on 2-dose schedules, options for recommendations have been discussed by the WG. There two basic approaches that could be taken by ACIP. One is to consider HPV9 as a 3-dose schedule and to wait to consider 2-dose schedules when data are available from the ongoing 2- versus 3-dose trial for 9-valent vaccine. The other option is to consider 2-dose schedules now for HPV2 and HPV4 based on available data.

To review some considerations for 9-valent vaccine (HPV9) that pertain to both options, in the BLA submitted to FDA in December 2013, there are data from 3-dose schedule in females 9 through 26 years of age and males 9 through 15 years of age. In contrast to the situation with PCV7 and PCV13, HPV4 likely will continue to be available for 12 to 18 months after HPV9 is licensed. This differs from the situation with the PCV7 to PCV13 transition and impacted the WG's proposed wording. The WG considered HPV9 for currently recommended ages in the US. However, because of the age groups included in the original BLA, HPV9 is expected to be licensed first for females 9 through 26 years of age and males 9 through 15 years of age. Use in males older than age15 would be off-label initially. Immunogenicity data in males 16 through 26 years of age were presented to ACIP earlier in this session. These data would be used to support licensure in the older aged males. The WG also considered that HPV9 would provide little additional benefit for males compared with HPV4. However, programmatic issues were considered by the ACIP WG, such as stocking different vaccines and the need to have different HPV vaccines for different age groups or sexes.

The first option is to consider HPV9 as a 3-dose schedule and to consider 2-dose schedules when data are available for this vaccine. In the draft wording that follows, the first two bullets are the same as the current recommendations and state the vaccination ages. The third bullet differs, with HPV9 included as one of the vaccines that can be used for vaccination of females or males. The last bullet states the 3-dose schedule:

Option 1

- ACIP recommends routine HPV vaccination at age 11 or 12 years for females and males. The vaccination schedule can be started beginning at age 9 years.
- Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been previously vaccinated. Males aged 22 through 26 years may be vaccinated.

- ❑ Vaccination of females is recommended with HPV2, HPV4 (as long as this formulation is available) or HPV9. Vaccination of males is recommended with HPV4 (as long as this formulation is available) or HPV9.
- ❑ A 3-dose schedule is recommended with the second dose 1-2 months after the first dose and the third dose 6 months after the first dose.

To conceptualize the recommendations, the following table shows what this recommendation would look like. It is essentially the current recommendation with HPV9 as one of the options for vaccination for females and males. At the bottom is a note about what part of this recommendation is off label:

Table for Option 1
HPV9 as 3-dose schedule and wait to consider 2-dose schedules

Routine	Those not previously vaccinated
Females and males 11-12 years	Females 13-26 years Males 13-21 years
3-dose schedule (0,1-2, 6 mos)	3-dose schedule (0,1-2, 6 mos)

Females: HPV2, HPV4 or HPV9
Males: HPV4 or HPV9

- HPV9 off-label for males older than age 15; data available

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Many other parts of the recommendation would need to be drafted. The following example shows some of the additional proposed wording that would be included for any option:

- ❑ HPV2, HPV4 and HPV9 all protect against HPV types 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States. HPV9 targets 5 additional cancer causing types, which account for about 15% of cervical cancers in the United States. HPV4 and HPV9 also protect against HPV types 6 and 11, types that cause genital warts.
- ❑ For protection against genital warts in addition to cancer causing HPV types, vaccination is recommended with HPV4 or HPV9. When HPV4 is no longer available, HPV9 can be used to complete a series begun with HPV4.

The second option is to consider 2-dose schedules for HPV2 and HPV4 in 9 through 14 year olds based on available data. If this is considered, there are three options for HPV9 if that vaccine is licensed. The WG considered the first suboption. For the second suboption, the WG felt that there are no data, but a trial is ongoing and data will be available in less than one year. Regarding the third suboption, to postpone a recommendation for HPV9 until data from 2-dose trial, the WG had concerns about delay in vaccination waiting for HPV9 availability if this approach was taken.

Following is the second option considered by the WG, which is a 2 dose schedule for HPV2 and HPV4 in 9 through 14 year olds and a 3-dose schedule for HPV9. For this recommendation, the first part of recommendation would be the same as the current recommendations. As in Option 1, HPV9 would become one of the recommended vaccines. The second bullet addresses the different schedules. If the vaccination series is started with HPV2 or HPV4 before age 15 years a 2-dose schedule (0,6 months) is recommended. If the vaccination series is started with HPV9 before age 15 years, a 3-dose scheduled is recommended (0,2,6 months). If the vaccination series is started with any HPV vaccine at 15 years or older a 3-dose schedule is recommended (0,1-2 and 6 months):

Option 2

- ❑ Vaccination of females is recommended with HPV2, HPV4 (as long as this formulation is available) or HPV9. Vaccination of males is recommended with HPV4 (as long as this formulation is available) or HPV9.
- ❑ If the vaccination series is started with HPV2 or HPV4 before age 15 years a 2-dose schedule is recommended (0,6 months). If the vaccination series is started with HPV9 before age 15 years, a 3-dose scheduled is recommended (0,2,6 months).
- ❑ If the vaccination series is started at age 15 years or older with any HPV vaccine a 3-dose schedule is recommended (0,1-2 and 6 months).

It is important to note that the 9 through 14 year old age group is the age group included in the bivalent trials of 2 doses. The one study available for HPV4 included girls 9 through 13 years, but the ongoing 9-valent trial includes girls 9 through 14 years.

A variation of Option 2 would be to recommend HPV9 in a delayed 3-dose schedule so that the first and second doses would be similar to the 2-dose schedule. As was presented to the WG in June 2014, for HPV2 and HPV4, 3-dose schedules with longer intervals between doses have been found to be non-inferior to the currently recommended schedule. The following show Options 2 and 2a in table format:

Routine	For those not previously vaccinated
Females and males 11-12 years	Females and males 13-14 years
HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,2,6 mos)	HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,2,6 mos)
	Females 15-26 years and males 15-21 years
	HPV2, HPV4, HPV9: 3-doses (0,1-2, 6 mos)
Females: HPV2, HPV4 or HPV9 Males: HPV4 or HPV9	
<ul style="list-style-type: none"> ▪ Off-label for 2-dose schedules for HPV2, HPV4; HPV9 for males 16-21 years ▪ Data available for all schedules and vaccines 	

Routine	For those not previously vaccinated
Females and males 11-12 years	Females and males 13-14 years
HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,6,12 mos)	HPV2 or HPV4: 2-doses (0,6 mos) HPV9: 3-doses (0,6,12 mos)
	Females 15-26 years and males 15-21 years
	HPV2, HPV4, HPV9: 3-doses (0,1-2, 6 mos)
Females: HPV2, HPV4 or HPV9 Males: HPV4 or HPV9	
<ul style="list-style-type: none"> ▪ Off-label for HPV2, HPV4 and HPV9 delayed schedule; HPV9 males 16-21 yrs ▪ No data available for HPV9 delayed schedule 	

There are pros and cons to each of these options. The WG felt that Option 1 was the simplest, given that there would be less confusion for providers and the public. Reconsideration can be given to 2-dose schedules when the 2-dose trial data are available for HPV9. In terms of Option 2, there is general interest in 2-dose schedules. These could facilitate delivery and decrease resources. This might also increase initiation, although there are no data on this issue. In the current situation, there is concern about potential for confusion for providers if there are different recommendations for different vaccines and frequent changes in recommendations. There is the remaining question about differences in duration of protection for 2 versus 3 doses. In addition, a 2-dose schedule would be off-label for HPV2 and HPV4 and manufacturers have no plans for submission to FDA for these.

In conclusion, Dr. Markowitz posed the following questions:

- Are there other recommendation options that ACIP members want to consider?
- What other data would ACIP members want to see before February 2015 or during the February 2015 ACIP meeting?
- Which option do ACIP members prefer?

Discussion Points

Dr. Vazquez asked about revaccination of individuals who are fully vaccinated with quadrivalent vaccine.

Dr. Markowitz replied that the WG is not enthusiastic about revaccination recommendations. They are still exploring some of the cost-effectiveness issues. As shown by Dr. Brisson, it does not appear that this would be cost-effective in the most favorable scenario. The WG also feels that resources should be spent on vaccinating more people. Therefore, the decision was made not to make a specific recommendation for revaccination at this time.

Dr. Harrison liked the simplicity of Option 1.

Dr. Kempe also like the simplicity of Option 1. She pointed out that it would be extremely difficult to ignore the 9-valent vaccine and not make a recommendation about that. If that is the case, it means potentially 3 different vaccines with different dosing patterns. That will be very difficult.

Dr. Bennett agreed with the simplicity argument, but expressed concern that if Option 2 was selected and the 9-valent study later shows inferior immunogenicity with 2 doses, they would be stuck forever. In terms of a pathway, it is important to deal with implementation of the 9-valent vaccine and then figuring out the number of doses.

Ms. Pellegrini thought there would be simplicity in Option 1 in terms of providers, but for families there is less simplicity to a 3-dose schedule than a 2-dose schedule. There is also the consideration that if ACIP recommends 3 doses, they have to be cognitive of the fact that they may have to revise the recommendation a year later to 2 doses. That has implications for how people view ACIP's work.

Picking up on that point, Dr. Temte said he could see a benefit eventually in leveraging the biology of younger people into something that has profound effects. It will send a powerful message to parents to tell them that if they begin this series before the age of 15, only 2 doses will be needed, but if they begin it after that, 3 doses will be needed. This could result in a profound increase in rates.

Dr. Bennett asked if Ms. Pellegrini and Dr. Temte were saying to make a recommendation “out of the box” with only 2 doses for 9-valent.

Dr. Temte emphasized that he would “eventually” like to see that. They do have to be careful not to pre-anticipate the results of studies being conducted. If such results are found, he would be very proactive in regard to the benefit for families.

Dr. Schuchat reminded everyone that the results that might be forthcoming in a year or so regarding a 2-dose schedule will be about a 0, 6 month interval not a 0, 2 month interval. In addition to whatever sequencing and timing is determined, she does not think the science suggests that 0,2 is the same as 0, 6.

Dr. Kempe agreed that having the option of 2 doses if starting early could be a very strong leverage. She also agreed that flip-flopping a lot on recommendations has the potential to destroy credibility. That is a strong case for recommending the 3-dose schedule for 9-valent vaccine, but making the transition as quickly as possible to 2 doses.

Dr. Riley’s concern with recommending 2 doses at this point regarded whether that was appropriate since they are awaiting completion of the studies. Also, it was not clear to her whether there would be any data regarding the length of protection from 2 doses.

Ms. Pellegrini clarified that making recommendations with little or no evidence would always be her last choice, but there was a prospect of having evidence in the near future. She was not trying to say that they should presume what the evidence would be, but instead was suggesting that they build into the recommendations the recognition of that and strongly telegraph that changes may be coming soon.

Dr. Reingold liked the simplicity of the first option, but pointed out that the duration of protection of a 3-dose schedule is also not known.

When thinking about HPV vaccines, to Dr. Karron there is always the question of what can be assumed by inference from 4-valent versus 9-valent. She was not personally convinced that they would need to wait for long-term duration data for 2 doses to be able to move to a 2-dose schedule. They might be able to use data from the quadrivalent vaccine by inference to think about that. She agreed that it would be helpful to have the initial efficacy data from the 2-dose schedule for the 9-valent vaccine.

Dr. Bolongia thought the incremental cost-effectiveness analysis was very helpful, which was done on 3 doses. If he recalled correctly, it was not particularly sensitive to the duration of protection. While it would be great to go to 2 doses, the science did not seem to support that yet.

Dr. Brisson replied that duration of the protection was assumed to be the same for the 4-valent and 9-valent vaccine, and the analysis was not sensitive to that assumption.

Dr. Middleman (SAHM) pointed out that it is important to recognize that the majority of those who start the HPV vaccination series complete it. She was not sure whether 2 doses versus 3 doses should become a major issue. More important is how to get people to start the series. There was a 2-dose recommendation for a specific age group for the Hepatitis B vaccine for one of the products, which she thought became very confusing. It is important to remember the historical perspective.

Dr. Schuchat reminded everyone that in the early days of Hib vaccine, there were different vaccines with difference schedules that providers had no problem with because they were so enthusiastic about an effective Hib vaccine.

Dr. Temte pointed out the importance of better understanding why only 50% of potential recipients choose to get the first dose. He agreed that once the first dose is given, the series is usually completed. However, that is only 1 out of 2 people. He is much more interested in having the first dose provided at age 11, 12, or 13 than at age 18, 19, or 20. There are some profound effects in terms of how to market this vaccine. While it is not ACIP's job to market vaccines, it is their job to keep in mind what practitioners face on a daily basis in trying to implement ACIP's recommendations.

Regarding off-label use, Dr. Pickering asked whether studies are being conducted to clarify whether there would be any data forthcoming on the 2-dose 0,12 months 9-valent vaccine. That would fit in nicely with the yearly recommendations adolescents have for their visits.

Dr. Markowitz replied that the 9-valent trial currently being conducted does have a 0, 12 month arm, so there will be data. One of the trials conducted with a bivalent vaccine, which is not published yet but has been presented, also had a 0, 12 month arm. That study showed that the 0,12 month results looked about the same as 0, 6 months. They were both non-inferior to the older women. Those data have only been presented at a meeting. Most of the studies have been on a 0,6 month schedule. The reason she highlighted in the tables what would be off-label was because she wanted to point out for ACIP that in any of the scenarios proposed, there would be at least one off-label recommendation. In order for Option 1 not to have an off-label component, they will have to recommend the quadrivalent vaccine for 16 through 26 year old males until the 9-valent vaccine is licensed in that age group. Even though the simplest recommendation will contain an off-label component for older males, that is temporary because Merck is going to be submitting the data presented during this session to FDA. However, it will take the usual amount of time to be reviewed by FDA. If ACIP recommends bivalent or quadrivalent 2-dose schedules, those will remain off-label because the companies are not submitting any data to the FDA on the bivalent and quadrivalent vaccines.

Dr. Temte asked whether the members had given Dr. Markowitz sufficient feedback.

Dr. Markowitz said they had, but she wanted to understand more about the comment that was made regarding giving people some foresight into what is coming and how they recommend doing that.

Ms. Pellegrini said she would be delighted to discuss that offline.

Dr. Ault (ACOG) was glad to hear people talk about pragmatic issues. One pragmatic issue that gynecologists have to deal with every day is that they are not seeing patients in the earliest teen years. If there is a 2-dose schedule, payers will only pay for 2 doses. People will leave the office with zero doses if they think they have to pay for the extra third dose.

Dr. Temte noted that there had been some recent changes on recommendations for annual gynecologic exams. He asked Dr. Ault how common it is for women to present every 12 months as opposed to sporadic visits in between. He also asked AAFP and AAP to weigh in on their abilities to carry out the current 0, 1-2, 6 month schedule versus a 0, 12 month schedule.

Dr. Ault (ACOG) responded that there are still recommendations about mammographies, breast exams, blood pressure checks for people using oral contraceptives, pregnancy planning, et cetera that probably got short shrift during the annual exam when the concentration was on the Pap smear. The well-woman visit is being reviewed by ACOG. As a specialty, they could certainly do a better job with immunizations as well.

Dr. Loehr (AAFP) responded that logistically he has turned it into a 0, 6-week, and 6-month schedule because the two 6s make it easier for his staff and patients to remember. The 6-week visit is very easy for people because it is not that far away. The 6-month is much harder and is usually caught up at the next well-child check when missed.

Dr. Kimberlin (AAP) said that clearly 2 visits would be simpler than 3 for an adolescent. That said, he believes the AAP would rather wait for the pending data that can drive the discussion and decision.

Dr. Temte concluded that there seemed to be a consensus that a 2-dose schedule is something to strive for in the future, but until data and evidence are available, they are hesitant to take that leap. While there may be some incrementalism, it should be evidence-based incrementalism.

Dr. Middleman (SAHM) clarified that SAHM would agree with that process. The concern about 2 doses for one product at one time is an issue, and she just wanted to make sure that people were clear on SAHM's position on that.

Public Comment

Dr. William Schaffner National Foundation for Infectious Diseases

On behalf of the National Foundation for Infectious Diseases (NFID), I am pleased to announce a new Call to Action from NFID and the Council of State and Territorial Epidemiologists (CSTE) that urges healthcare professionals to be stronger advocates for HPV vaccination. A hardcopy of the report was included in the packet for ACIP members and liaisons, and additional copies are on the handout table outside the room. It is troubling to NFID and to me personally, and I hope to all of you, that extremely effective HPV vaccines are available but are still underutilized, leaving adolescents vulnerable to HPV-related cancers. The Call to Action is supported by many professional organizations. Among its conclusions, healthcare professionals need to recommend HPV vaccine with the same strength and conviction that they recommend other adolescent vaccines—same day, same way. It is their responsibility to educate themselves and everyone in their practice about HPV and the benefits of vaccination so that positive messages reach their patients and, of course, parents. Finally, a drum we beat often, they need to make

HPV vaccination routine and eliminate missed opportunities. First dose coverage in girls and boys 13 through 17 would reach over 90% if they received HPV vaccine at the same time they received other recommended vaccines. The Call to Action is available on NFID's new HPV Resource Center. The website is available in the document. The resource center includes tools from a range of medical organizations to help healthcare professionals improve HPV vaccine delivery. Finally, NFID and CSTE will be hosting a series of webinars, with the first scheduled for November 4th, to share the report and its findings. Information about the webinars and a link to the register is available at the HPV Resource Center website and on a card, some of which may still be on the handout table. Thanks. The link to the HPV Resource Center is: <http://www.adolescentvaccination.org/hpv-resource-center>.



Day 2: Public Comment

No public comments were offered during this session.



Certification

Upon reviewing the foregoing version of the October 29-30, 2014 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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